The significance of systemic hypertension before and after pregnancy

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Thesis Abstract

Preeclampsia is a common pregnancy condition characterised by extensive acute systemic vascular changes which are traditionally thought to resolve postpartum. Preeclampsia is also associated with increased risk of premature maternal cardiovascular disease; however, the exact nature of this association is currently unknown. This thesis presents findings exploring the links between hypertension in pregnancy and future maternal cardiovascular disease, by evaluating persons affected by hypertension in pregnancy for cardiovascular risk factors and persisting subclinical vascular changes in the postpartum period.

Postpartum women were assessed for novel and traditional markers of cardiovascular risk and vascular dysfunction using non-invasive techniques. Hypertension in pregnancy was associated with a higher prevalence of persisting hypertensive abnormalities on both office and ambulatory blood pressure measurement, as compared to women with normotensive pregnancy. Factors contributing to high rates of postpartum uncontrolled hypertension were investigated, and poor medical follow-up after delivery and inaccurate birth medical records were implicated.

Potential strategies to improve follow-up after complicated pregnancies were examined through community-based nurse-initiated maternal health screening. Incorporating maternal health checks into routine child health nurse visits proved feasible, and demonstrated that 1 in 10 women screened had abnormal findings resulting in referral for further follow-up.

The potential significance of identifying hypertension prior to pregnancy was explored through evaluating pregnancy outcomes in women with known chronic hypertension prior to pregnancy. Rates of preeclampsia and major maternal and neonatal morbidity were significantly increased in chronically hypertensive versus normotensive women, however not all morbidity could be attributable to superimposed preeclampsia.

Clinical risk factors present in early pregnancy for superimposed preeclampsia were explored in women with chronic hypertension. Historical and non-modifiable risk factors including a past history of preeclampsia and a greater chronicity of hypertension, rather than potentially modifiable risk factors conferred the greatest risk.

In summary, this research has demonstrated increased rates of chronic hypertensive abnormalities after pregnancy affected by hypertension, thus increasing our understanding of how hypertension in pregnancy may be linked to long term cardiovascular risk. It also demonstrated suboptimal follow-up after hypertensive pregnancy, and provided a feasible avenue for improving follow-up through maternal health screening utilising a primary health service well-attended by the target population which already exists within current models of care. Finally, it has demonstrated that chronic hypertension is associated with adverse pregnancy outcomes in a local population, and risk factors for superimposed preeclampsia may be present prior to pregnancy. Hence, de novo identification of chronic hypertension either prior to, or after pregnancy may provide opportunity for further management and counselling regarding short term pregnancy risks and long term women's cardiovascular health.

Declaration

This thesis is an original work of my research and contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

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List of Abbreviations

ABPM	ambulatory blood pressure monitoring
ACC/AHA	American College of Cardiology/American Heart Association
ADIPS	Australasian Diabetes in Pregnancy Society
AH	antihypertensive medication
ALT	alanine aminotransferase
aOR	adjusted odds ratio
BMI	body mass index
BOS	Birthing Outcome Systems database
BP	blood pressure
CI	confidence interval
CKD	chronic kidney disease
CS	Caesarean section
DASH	Dietary Approaches to Stopping Hypertension diet
eGFR	estimated glomerular filtration rate
ELISA	enzyme linked immunosorbent assay
GDM	gestational diabetes
GH	gestational hypertension
HELLP	Haemolysis, Elevated Liver enzymes and Low Platelet syndrome
HDU/ICU	high dependency unit/intensive care unit
HREC	Human Research and Ethics Committee
HT	hypertension
IQR	inter-quartile range

ISSHP	International Society for the Study of Hypertension in Pregnancy
KDIGO	Kidney Disease Improving Global Outcome
MAP	mean arterial pressure
MCH	maternal and child health service
MPO	myeloperoxidase
OR	odds ratio
PE	preeclampsia
SCN/ICU	special care nursey/neonatal intensive care unit
SEIFA	Socio-Economic Indexes for Areas
sEng	soluble endoglin
sFlt-1	soluble fms-like tyrosine kinase 1
SGA	small for gestational age
VAED	Victorian Admitted Episode Database
VCAM-1	vascular cell adhesion molecule 1
VPDC	Victorian Perinatal Data Collection
WHO	World Health Organisation

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Chapter 1

INTRODUCTION

1.1 INTRODUCTION

Cardiovascular disease is the leading cause of death in Australian women, and the disease burden will likely continue to increase as the population ages (1). Strategies for identifying, predicting and modifying cardiovascular disease risk are crucial for improving future health outcomes and minimising healthcare expenditure.

Hypertensive disease in pregnancy is increasingly recognised as an important risk factor in the development of premature cardiovascular disease in women. Not only is pregnancy hypertension associated with increased risk of developing cardiovascular risk factors such as diabetes and hypertension in the long term, but also with identification of these risk factors at a young age either prior to, during, or soon after pregnancy (2-5).

The natural history of the development of both cardiovascular risk factors and cardiovascular disease in women from young adulthood through to advanced age remains largely unknown, as does how to best screen, risk-stratify and modify future disease risk. This makes optimal management and resource use somewhat challenging. That being said, pregnancy complications such as hypertensive disease may provide opportunity as an index event for identifying and targeting individuals at higher risk with further screening and potential intervention.

This literature review aims to outline the burden of cardiovascular disease in women, and cardiovascular risk factors and risk assessment in young women. Additionally, the impact of cardiovascular risk factors on pregnancy outcomes and development of cardiovascular disease after hypertensive pregnancies will be discussed with a specific focus on chronic hypertension.

1.2 CARDIOVASCULAR DISEASE AND RISK FACTORS IN WOMEN

1.2.1 Overview of cardiovascular disease in women

Cardiovascular disease is the leading cause of death for both men and women in Australia (6). Absolute risk rates are considerably lower in women than men at younger ages, however as age increases these risk rates converge (7, 8). Sexual dimorphism is

thought to account for a relative difference in 'biological age', exemplified by women tending to experience onset of cardiovascular disease on average 5-10 years later than men. However, as women tend to live longer than men, a higher number of women experience cardiovascular death overall in Australia per year as compared to men (6).

It is increasingly recognised that the same traditional cardiovascular risk factors contribute towards a higher relative risk of cardiovascular disease in women, as opposed to men with the same risk factors (7-9). For example, women with diabetes have a 40% excessive risk for the development or coronary artery disease than men with diabetes (10). Women are also demonstrated to have higher relative risk from smoking and hypertension for the development of myocardial infarction as compared to men (7, 10, 11). It is unclear if these observations are due to increased sensitivity of the female vasculature to insult and lasting damage relative to males, or whether other factors such as a delayed diagnosis and poor management of risk factors may be contributory (12).

In Australia, it has been observed that gender inequalities exist in the assessment and management of cardiovascular risk factors in primary healthcare (13, 14). In a cohort of 53,085 patients routinely attending primary healthcare services in 2012, women were less likely than men to receive adequate cardiovascular risk factor assessment and documentation. In the same study, women aged 35-54 years were also less likely to receive appropriate prescription of guideline-recommended medications when clear indications to modify cardiovascular risk were present, than their male counterparts or older women (13).

Sex disparity in the treatment and outcomes of women presenting with cardiac events has been noted internationally (8, 15). Women often present with more atypical symptoms and unusual lesions than men, leading to a higher rate of misdiagnosis and suboptimal evidence-based management on presentation (13, 16). As a consequence, women have been noted to have a higher rate of death due to cardiac episodes (17). Further to this, although mortality rates for coronary artery disease have generally declined over the past 30 years, rates remain largely unchanged in particular for women aged less than 55 years in the United States, Canada, and Australia (18-21).

These factors, combined with the observation that cardiovascular clinical trials and health research recruit a majority of male participants, highlight the ongoing need to better understand the pathophysiology, diagnosis and management of cardiovascular disease and risks factors in women (21-24).

1.2.2 Cardiovascular risk factors and young women

The pathophysiology of cardiovascular disease in women differs from men, and is reflected in the relative risk factors. Women experience both traditional cardiovascular risk factors such as hypertension, diabetes, metabolic syndrome, hypercholestolaemia, and smoking, but also factors specific to sex such as earlier menopause and menache, pregnancy hypertension, and gestational diabetes.

Little is known about the optimal management and natural history of the development of cardiovascular risk factors in pre-menopausal women. Risk factors are relatively uncommon in this group, and a large temporal delay often exists prior to development of clinically overt disease which makes research to determine benefit of both primary prevention and screening challenging. This is somewhat sobering when considering the potential for long and cumulative exposure to risk factors over a lifetime that young people may experience.

1.2.2.1 Chronic hypertension

Hypertension is the single-strongest contributor to the burden of disease worldwide according to the World Health Organisation. Others have also suggested that hypertension is “the most serious, neglected health problem for women in both the developing and developed worlds” (25). In Australian women, hypertension is associated with a 3-fold increased mortality and is less well-controlled as compared to men in the same population (1). Additional to this, hypertension contributes to excessive mortality in women as compared to men with the same degree of hypertension. That being said, women with hypertension and metabolic syndrome have been shown to exhibit a higher

reduction in coronary events compared to men when achieving adequate blood pressure control (26).

Chronic hypertension has traditionally been regarded as a disorder of the sympathetic nervous system and renin-angiotensin-aldosterone system, and how they together regulate cardiovascular function and salt and water balance. However, the important contributions of immune system mechanisms to this picture are increasingly acknowledged (27).

Hypertension causes cardiovascular disease and death through a number of mechanisms. With time, hypertension causes various blood vessel adaptions in different vascular beds and organs, leading to end-organ dysfunction and damage (28, 29). Endothelial activation and dysfunction through inflammatory and oxidative pathways can lead to vascular remodelling, vascular stiffening, and atherosclerosis (30, 31). Additional immune and neurohormonal mechanisms can trigger cellular activation, release of mediators and antibodies, and contribute to vascular constriction and subsequent endothelial damage (27, 32, 33).

Blood pressure is known to remain relatively stable in women from late adolescence through to menopause, with a slight increase from around age 35 years. After menopause, there is a steady increase in blood pressure each decade, until rapid increase occurring in the eighth and ninth decades (34, 35). The association between menopause and blood pressure rise is also observed in women with premature ovarian failure (36). It is thought that the vasoactive modulatory effects of ovulation-related endogenous oestrogen and progesterone explain this observation, however exogenous replacement in postmenopausal women has been inconsistent in producing benefits in lowering blood pressure (37-40). Type of oestrogens or progesterone used may be a factor in the observed inconsistent findings (41).

Prevalence of hypertension amongst younger women varies greatly depending on population and data source used, and the fact that young women tend not to have blood pressure routinely measured so the diagnosis of hypertension is often incidental. Large and recent studies of culturally diverse women aged 18-39 years in the United States have shown the prevalence of stage 2 hypertension to range from 4.2-6.1% (42-

44). In Australia, data from a large national screening program revealed rates of uncontrolled hypertension to be 6.7% in women aged 18-24 years, 8.2% in 25-34 year-olds, and 13.9% in 35-44 year-olds (45). Conversely, rates of documented chronic hypertension from population data of women experiencing pregnancy are quoted to be significantly lower at 0.6% in Australia, and 1.76% in the United States (46, 47). These source databases have been independently validated and are known to under-report the prevalence of chronic hypertension in this population by a magnitude of around 3 to 4-fold which may contributory to the observed discrepancy (47, 48).

Many factors in addition to menopause are known to influence blood pressure in younger women up to middle-age. Genetics, secondary causes of hypertension, oral contraceptives, pregnancy and preeclampsia, lactation, assisted reproductive technologies, body fat mass, and lifestyle factors such as diet, alcohol intake, and level of physical activity (49, 50). It is likely that a combination of risk factors leads to the development of hypertension in a majority of individuals. Body weight in particular is an important cofactor, with obese and overweight body sizes correlating with a 2 to 6 - fold increase in risk of hypertension in women (51). Hypothetical modelling determining the relative contribution of specific common risk factors to the development of hypertension in women has found obesity to have the strongest impact both in isolation, and in combination with other risk factors (52).

Pathogenesis of hypertension in younger women likely differs with age of onset. While essential hypertension is likely the commonest overall cause, young adult women and adolescents have a significantly higher proportion attributable to secondary causes. Children and adolescents for example typically have an identifiable cause in 85% of cases (35). Prevalence of secondary hypertension amongst slightly older and postpartum women has been quoted at 10-14% (53, 54). This however, is likely to be an underestimation as many young women either do not undertake or have incomplete secondary hypertension screening (53, 55). Additionally, women with secondary hypertension may be underrepresented in the pregnancy population due to difficulty conceiving.

Sympathetic nervous system overactivity is likely to explain a large proportion of essential hypertension in younger women, particularly in the presence of obesity. Oestrogen is thought to have beneficial effects in regulating sympathetic nervous system activation, and thus lower hypertension risk. However, the regulating effects of oestrogen in sympathetic nervous system pathway are abrogated by obesity, inflammation and stress (56).

The diagnosis and treatment of hypertension in younger women does not currently have a strong evidence-base to guide management. Blood pressure is known to have a continuous relationship with cardiovascular risk through the spectrum of hypertension down to normotensive levels. Traditional thresholds to diagnose hypertension and guide management are extrapolated from data in older populations, and consequently guidelines tend to make 'general' or 'expert' recommendations (43). Blood pressure treatment thresholds and treatment targets are used in the general population to identify and modify future disease risk, and are based on longitudinal interventional studies with clinically relevant endpoints. Similar longitudinal studies including younger women are scarce, and current knowledge regarding the significance of elevated blood pressure in this population is limited to observational data (57, 58). As an example, elevated blood pressure in young adulthood has been shown to correlate with later cardiovascular disease and mortality, independent of blood pressure control later in life (59). However, the effect of lowering blood pressure in young adulthood on future disease risk remains unknown. This example does however still emphasise the significance of blood pressure in this population, and highlights current gaps in knowledge for improving future management such as defining treatment thresholds for risk stratification and modification.

In the absence of both a strong indication for aggressive pharmacotherapy or a clear evidence-base for treatment, lifestyle modification is likely the safest and best-tolerated approach to controlling blood pressure in young women, especially for those with mild essential hypertension. Prescribing lifestyle modification may also have benefit in improving coexisting risk factors such as diabetes and obesity. Lifestyle interventions with evidence for improving blood pressure in young adults include dietary modification, reducing alcohol consumption, increasing physical activity and weight loss (60, 61).

Dietary modifications include a reduced sodium or DASH-style (Dietary Approaches to Stop Hypertension) diet, or a Mediterranean diet high in polyphenol-rich olive oil (62-64).

1.2.2.2 Diabetes

Both type 1 and type 2 diabetes are strong and independent cardiovascular risk factors in Australian women. Diabetes in women presents a high excessive risk of cardiovascular death and disease as compared to men, especially if coexisting with additional risk factors such as smoking or hypertension (13, 65).

Diabetes causes progressive vascular dysfunction through a number of pathologic mechanisms over time, leading to premature vascular aging (66, 67). Coexisting metabolic syndrome, obesity and hypertension have been shown to accelerate the pathologic changes of diabetes with time (68, 69). Early diagnosis, good glycaemic control, and aggressive management of coexisting cardiovascular risk factors have been shown to reduce the long-term disease burden (67, 70).

Aside from obesity, important risk factors for the development of type 2 diabetes in younger women include a family history of diabetes, a history of gestational diabetes, polycystic ovarian syndrome, medications such as corticosteroids, and ethnicity. Ethnicity is of particular relevance to the multicultural Australian population, with indigenous Australians, Maori, Asian, South Asian, Pacific Islander, Middle Eastern and non-white African displaying increased risk (71).

Type 2 diabetes is of relatively low prevalence amongst women of childbearing age at 0.5% in Australia (72). However, risk of developing type 2 diabetes is increased in the long term for women who experience any of the three most common maternal medical conditions in pregnancy: gestational diabetes, obesity or pregnancy hypertension (3, 4, 73). After gestational diabetes, women have a 30% risk of recurrence in any subsequent pregnancies, and a 50% risk of developing diabetes in the next 10-30 years (74). Accordingly, the Australasian Diabetes in Pregnancy Society recommends that women

with gestational diabetes undergo regular individualised long term surveillance for the development of type 2 diabetes, starting from 6-12 weeks after birth (71).

Management of diabetes in young women is focused on achieving good glycaemic control and aggressive management of coexisting risk factors. This may include strategies such as weight loss and dietary modification, or antihypertensive therapy. For those with type 2 diabetes and elevated body mass index, lowering body weight through dietary modification and exercise can reverse the presence of diabetes in some individuals.

1.2.2.3 Obesity

Within Australia, 55% of all women are currently overweight or obese, with 37% of women aged 25-44 being obese (6, 75). Further to this, data from the Australian Longitudinal Study on Women's Health has shown a dramatic generational increase in the proportion of women with obesity, and that obesity onset occurs at a younger age with each generation (76). Obesity is also demonstrated to strongly correlate with socioeconomic disparity and disproportionately affect specific groups in Australia including indigenous women, women residing in regional and semi-rural areas, and migrants to Australia (77).

Many genetic, lifestyle, physical health and psychosocial factors can contribute to the development of obesity. In young Australian women, low levels of physical activity, poor diet, large weight gain during pregnancy, mental health and sociodemographic factors are implicated in the increasing national rates of obesity (77).

Obesity is thought to increase cardiovascular disease risk through a number of independent mechanisms which lead to alterations in cardiovascular system function (68, 78). Obesity has been observed to induce a chronic low-level inflammatory state leading to endothelial activation and dysfunction, and can generate a chronically elevated cardiac output causing gradual increase in vascular stiffness and cardiac hypertrophy (78). Importantly, obesity is generally considered a modifiable risk factor for future disease. Obesity often also coexists with other disease processes such as the

metabolic syndrome, hypertension and diabetes which can in turn compound cardiovascular risk due to obesity.

As body fat mass increases, a proportional increase in risk of cardiovascular disease has been observed in women (79). The Framingham Offspring Study has demonstrated longitudinal evidence of the independent association between risk of future cardiovascular disease and mortality, and obesity in women from young adulthood (80, 81).

Management of obesity is focussed on investigation and management of underlying causes or contributing factors, and strategies for weight reduction. Exercise, dietary education and modification, bariatric surgery and pharmacotherapy have been shown to improve obesity in different populations. There is a paucity of high-quality trials evaluating weight loss interventions specific to younger women (82). Behavioural interventions are the cornerstone of management for younger women, with weight-loss surgery reserved for refractory cases with significant morbidity.

1.2.3 Cardiovascular risk factor assessment and in young women

1.2.3.1 Application of risk prediction tools in young women

In the general population, cardiovascular risk assessment provides valuable guidance on evidence-based interventions for individual risk factors to modify risk of future disease. Risk assessment often includes evaluation for a number of additional risk factors, and can also involve the use of risk prediction tools to estimate the magnitude of risk for developing significant disease over the proceeding 10 or 30 years. However, cardiovascular risk assessment and the use of risk prediction tools to guide management in younger women is somewhat problematic. Absolute prevalence of cardiovascular disease is invariably low in young women, thus a detailed cardiovascular risk assessment is rarely performed unless a specific event has occurred or a risk factor is identified incidentally. Examples of specific events which may trigger a formal cardiovascular risk assessment include preeclampsia or a new diagnosis of chronic hypertension.

Preeclampsia in particular is a relatively common occurrence among young women, and can be associated with significant maternal morbidity. Globally, preeclampsia affects around 1 in 20 women however definitions vary making incidence estimation difficult (83). Preeclampsia is now strongly linked with increased probability of developing a range of cardiovascular risk factors and premature onset of cardiovascular disease (2, 3). In recognition of this, the American Heart Association published the first guideline in 2011 to recommend a history of pregnancy hypertension be included in the cardiovascular risk assessment of women (84).

As awareness increases linking preeclampsia to future cardiovascular disease, attempts to use existing risk prediction tools or devise new tools are being made to guide future management and optimisation of health in these women. As discussed above, useful application of risk prediction tools to this population is limited as risk estimation is often very low despite presence of significant risk factors. Additionally, there is an absence of longitudinal trial data to guide appropriate management. With this in mind, some groups have proposed guiding management by calculating relative cardiovascular risk for age rather than absolute risk, or recommended calculating risk estimates as though young women were 60 years of age (43, 85, 86). Validity of these techniques remains uncertain.

Specific to the Australian population, both the 1991 Framingham and 2013 PCE-ASCVD 10-year cardiovascular risk prediction tools have been validated in women from an age of 40 years and above. It is important to note however that cardiovascular risk was on average overestimated, and generalisability to younger women is limited as only a small number of cardiac events occurred amongst younger women within the study (87).

Postpartum risk screening and prediction using traditional cardiovascular risk factors and tools has been shown to identify a number of women with increased risk, especially after preeclampsia (4, 88-90). Long term validity of these risk prediction tools in this population remains uncertain, and existing data is extrapolated from registries, longitudinal cohorts, and survey data. Additionally, it is important to note that while traditional cardiovascular risk factors and abnormal risk screening are prevalent after preeclampsia, many aspects of the preeclampsia and cardiovascular event-relationship

are somewhat atypical, especially in the first decade after pregnancy. Hypertension in pregnancy is associated with an increased risk of cardiovascular events from immediately after birth, even in the absence of traditional cardiovascular risk factors (91). Additionally, women with a history of preeclampsia have increased risk of stage B asymptomatic heart failure at 1-2 years postpartum, and an increased risk of atypical coronary lesions in the 10 years after an affected pregnancy (92). These atypical cardiovascular associations highlight the uncertainty and complexities in understanding the underlying pathogenesis of long term disease and predicting cardiovascular risk after preeclampsia. Accordingly, focussing on traditional risk factors and screening tools rather than broadly exploring this area may limit future progression in understanding the cardiovascular disease link and modifying future disease.

1.2.3.2 Characterisation of blood pressure with ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM), usually over a 24-hour period is currently the gold standard for evaluation of blood pressure (93). ABPM provides ability to characterise circadian blood pressure changes and determine the presence of masked hypertension and other abnormalities which may not be detected by routine office blood pressure measurement. ABPM is also demonstrated to provide greater sensitivity and accuracy than office blood pressure measurement in predicting hypertension-mediated organ dysfunction, cardiovascular events, and mortality (43).

Limitations exist with the use of ABPM. Although blood pressure readings derived from ABPM are more reproducible than office blood pressure measurement, ABPM has been shown in some individuals to display variability and limited reproducibility, particularly relating to night-time blood pressure assessment (94-97). This is not unsurprising considering the many factors which impact blood pressure variability in daily life. For individuals who do not tolerate ABPM, home blood pressure monitoring following a standardised protocol can be a useful substitute, and has the added benefit of being lower in cost than ABPM (43).

Masked hypertension is an important finding on ABPM and is characterised by an office blood pressure measurement below the threshold for stage 2 hypertension (<140/90 mmHg), combined with an average awake blood pressure demonstrating hypertension (>135/85 mmHg) (43). Masked hypertension is known to be of higher prevalence in younger individuals, those with anxiety and a higher level of work-related stress, obesity, chronic kidney disease, and diabetes (98, 99).

In the general population, masked hypertension has been shown to strongly correlate in multiple meta-analyses with incidence of cardiovascular events (100, 101). Cardiovascular event risk in untreated masked hypertension is substantially higher than normotension and white-coat hypertension, however is not as high as for sustained hypertension. For those on antihypertensive therapy, cardiovascular event rates are comparable for masked hypertension and sustained hypertension.

Longitudinal studies of masked hypertension in the general population suggest progression to sustained hypertension occurs in around a third of individuals, and resolution to normotension in another third over a 5-year period (102). Importantly, there is currently no longitudinal evidence on the effect of antihypertensive therapy on cardiovascular outcomes in any population with masked hypertension (43).

ABPM is also able to characterise the pattern of white-coat hypertension. White-coat hypertension exists when normotension is present on ABPM, however hypertension is measured on office blood pressure measurement. Mechanisms of the 'white-coat' effect remain uncertain, however increased adrenergic activity has been observed in persons with white-coat hypertension as compared to normotensive people.

White-coat hypertension is no longer dismissed as an innocent condition, but rather, a condition associated with metabolic risk factors, asymptomatic organ damage, and a high risk of progression to sustained hypertension (103). Cardiovascular event risk is also increased over the mid to long-term compared to normotension as outlined in the PAMELA study (104).

White-coat hypertension is also of importance in younger women. It is known to be of proportionately high prevalence in this age group as compared to other blood pressure

patterns, demonstrating the potential utility of ABPM in young women prior to initiating antihypertensive therapy. Additionally, white-coat hypertension in pregnancy has risk of progression to sustained hypertension, and can predict onset of preeclampsia in some populations (105). Optimal management of white-coat hypertension in young women remains unknown, however longitudinal monitoring seems appropriate given risk of progression to sustained hypertension.

Ambulatory blood pressure monitoring can also provide valuable information on circadian blood pressure changes. Blood pressure is known to naturally lower during sleep, and a loss of nocturnal blood pressure fall is associated with long term cardiovascular risk in multiple populations irrespective of daytime blood pressure levels. Long term adverse associations with loss of circadian blood pressure variation include target end-organ damage including cardiac hypertrophy, carotid media intimal thickening, cardiovascular calcification, and albuminuria (106, 107).

Loss of diurnal blood pressure variation has been associated with a vast number of medical conditions, psychosocial and lifestyle factors. Specific medical conditions include: uncontrolled or resistant hypertension, chronic kidney disease, diabetes, obesity, sleep disordered breathing, hyperuricaemia, and both overt and subclinical hypothyroidism (108-112). Psychosocial and lifestyle factors include: socioeconomic disparity and psychosocial stress, chronic anxiety, depression and post-traumatic stress disorder, insomnia and poor sleep hygiene, and shift-working (113-116).

Nocturnal 'non-dipping' is typically defined as a fall of less than 10% in average nocturnal blood pressure as compared to daytime average levels (43). Mechanistically, increased sympathetic activation and salt sensitivity have been postulated as contributory. To date, benefits of therapeutic modulation of nocturnal blood pressure dip remain unclear and are areas of ongoing research. Current guideline recommendations focus on investigation for potential underlying causes given the significant associations with endocrine, renal, cardiovascular and psychological disease (117, 118).

Prevalence of nocturnal non-dipping in younger women is not widely reported, but seems to vary between populations at 8-44% (119-121). Racial differences are observed

with a higher prevalence of non-dipping noted amongst African-American young women (120, 122).

In young women, nocturnal non-dipping has specifically been associated with polycystic ovarian syndrome, posttraumatic stress disorder, dysautonomia and orthostatic intolerance, and poor sleep quality (123, 124).

The longer term prognosis and disease associations with nocturnal non-dipping in younger women are largely unknown despite being well-studied in the general population. Longitudinal data from the CARDIA study examined the association between future vascular calcification and nocturnal blood pressure dip in 169 multiracial women who underwent ABPM at a mean age of 30 years. The proportionate fall in nocturnal blood pressure on ABPM correlated with degree of coronary artery calcification ten to fifteen years later with a U-shaped relationship (125). This suggests that absent or reduced dipping and extreme dipping may be of significance in younger women, although pathophysiologic mechanisms are uncertain.

In younger women, a number of lifestyle interventions have been evaluated for effect on nocturnal blood pressure dip. Weight loss in obese young women has been observed to improve nocturnal dip (126). Additionally, acute exercise has been shown to improve nocturnal dipping pattern in previously non-dipping pre-hypertensive women (127). Dietary salt modification is suggested to improve nocturnal dip in hypertensive women, however salt loading does not seem to increase nocturnal blood pressure in healthy normotensive young women (128, 129).

1.2.3.3 Biomarkers for cardiovascular risk

A number of biomarkers are establishing roles in the clinical prediction of cardiovascular disease and diagnosis of both overt and subclinical vascular dysfunction. The clinical utility of biomarkers can be limited by lack of specificity, however the ease-of-use relative to other techniques such as aplanation tonometry support ongoing clinical and research development.

Limited study into the long term utility of cardiovascular biomarkers in younger women has been undertaken, presumably due to the lower burden of disease in this population. However, preeclampsia is a common condition affecting younger women which is associated with elevation of a number of biomarkers, including biomarkers observed to have direct pathological effects on the vasculature (130). A number of biomarkers in preeclampsia have been implicated in the development of cardiovascular disease and cardiovascular risk factors in the general population. As such, investigation into the postpartum resolution or persistence of these biomarkers after preeclampsia may aid in understanding the links between preeclampsia and premature cardiovascular disease. Limited investigation into persistent postpartum biomarker abnormalities has been reported to date.

Soluble endoglin is a circulating hypoxia-inducible anti-angiogenic factor and inhibitor of TGF-β1 (transforming growth factor β1) typically found in high circulating levels in women with preeclampsia (131). Postpartum evaluation for persistent elevation of circulating levels is not yet reported.

Elevation of endoglin in the general population has been associated with obstructive sleep apnoea and nocturnal hypertension as measured by ABPM (132). In addition to associations with systemic hypertension, endoglin has been implicated in pulmonary hypertension and the development of cardiac fibrosis. High endoglin expression is observed in cardiac fibroblasts and endothelium of persons with end-stage heart failure, and selective inhibition of endoglin-mediated TGF-β1 signalling in animal models attenuates development of cardiac fibrosis (133). Clinical utility of measurement outside of pregnancy or benefit of therapeutic modulation remain uncertain.

Soluble sms-like tyrosine kinase 1 (sFlt-1) is a circulating anti-angiogenic factor and splice variant of vascular endothelial growth factor receptor-1. sFlt-1 is observed in high levels in preeclampsia and has significant evidence of direct pathologic effects (134). Therapeutic modulation by systemic removal has been observed to temporise features of the preeclamptic syndrome and prolong pregnancy (135). Elevated levels of sFlt-1 have also been observed in young adults outside pf pregnancy with malignant hypertension. Postpartum resolution of elevated sFlt-1 levels related to pregnancy and

preeclampsia have been investigated in a number of small studies (136, 137). No clear clinicopathological patterns have been reported to date, although levels are observed to remain elevated in a proportion of women after preeclmapsia.

Copeptin is a circulating inert pro-segment of arginine vasopressin. Copeptin is secreted simultaneously with vasopressin although has a longer biological half-life. As such, copeptin has utility as a surrogate marker for vasopressin release. Copeptin is typically considered to be a 'stress-biomarker' and sign of central neurohormonal activation, with elevated levels observed in situations of physical and psychological stress (138, 139). Elevated serum copeptin is demonstrated to be one of the first detectable abnormalities in early pregnancy in women destined to develop preeclampsia (140, 141). Postpartum characterisation of copeptin levels has not yet been reported in the context of pregnancy hypertension. Evaluation of postpartum copeptin levels after preeclampsia would be of specific interest as sleep disturbance, sleep disordered breathing, and hypertension have been associated with elevated levels, and lactation with reduced levels (142).

Although copeptin has been shown in the general population to be a sensitive predictor of cardiovascular disease which correlates strongly with disease severity, widespread clinical application is currently limited by reduced specificity (143-145).

Vascular cell adhesion moledule-1 (VCAM-1) is expressed in a variety of cells during inflammation and has a pathological role in endothelial cell activation and dysfunction. Elevated levels have been observed in women with preeclampsia, which has been shown to persist into the postpartum period in a small number of studies and appears to correlate with elevated body mass index (146, 147).

VCAM-1 has an established role as a marker of endothelial activation in human clinical studies. Although generally accepted as a predictor of cardiovascular disease, studies involving younger participants have not demonstrated improved prediction over traditional cardiovascular risk factors after adjustment for baseline factors (148). As such, its clinical utility in younger populations remains uncertain.

Myeloperoxidase (MPO) is an enzyme released by activated neutrophils and monocytes as an integral component of innate immune responses. MPO is considered to contribute towards vascular damage and inflammation at multiple stages of the atherogenic pathway (149). MPO is shown to be elevated in preeclampsia, however has not been proven to be predictive (150, 151). Evaluation of MPO in the postpartum period has not yet been reported.

Within the general population, serum or plasma myeloperoxidase levels are demonstrated to correlate in asymptomatic individuals with angiographic evidence of coronary disease and predict both myocardial infarction and cardiac mortality (152, 153). Myeloperoxidase in not well studied amongst younger adults, although increased levels have been observed in young smokers (154).

1.3 HYPERTENSIVE DISORDERS OF PREGNANCY AND CARDIOVASCULAR DISEASE

1.3.1 Overview of hypertensive pregnancy and future cardiovascular disease

Hypertension in pregnancy is an emerging and significant risk factor for future cardiovascular disease in both mother and offspring. A history of hypertension in pregnancy has been independently associated with increased risk of diseases such as chronic hypertension, ischaemic heart disease, stroke and chronic kidney disease (2, 155, 156). The relative risk of developing these cardiovascular diseases after preeclampsia is comparable to established cardiovascular risk factors such as smoking and diabetes (157). While cardiovascular disease and preeclampsia share many risk factors such as hypertension and genetic predisposition, it remains unclear whether shared risk factors explain the association or if preeclampsia is independently implicated in the pathogenesis of cardiovascular disease.

Although underlying pathophysiological mechanisms are uncertain, initial exploratory studies have given insight into how a history of preeclampsia and future cardiovascular disease may be linked. Human clinical studies have shown evidence of persisting endothelial dysfunction, subclinical inflammation, salt sensitivity, vascular remodelling, and autonomic nervous system dysfunction after preeclampsia (158). In addition to this,

increased prevalence of traditional risk factors for cardiovascular disease such as hypertension, hypercholesterolaemia, diabetes, and microalbuminuria has also been observed in women after preeclampsia (159-162). Important limitations of these studies are the wide variation in the time-point of assessment after birth, small sample size, and lack of longitudinal data. Ongoing work is needed to understand the natural history of subclinical cardiovascular abnormalities and cardiovascular risk factor development in this population with more clarity.

Emerging data from longitudinal cohort studies has shed some light on the time-course of cardiovascular risk factor development. Data from the PREVEND and Nurses' Health Study II suggest that risk of being diagnosed with hypertension occurs from soon after hypertensive pregnancy, and approaches a prevalence rate of 30% by age 40 (3, 4). Important limitations of these cohort studies are that both were reliant on self-reporting of hypertensive pregnancy.

1.3.2 Follow-up after hypertension in pregnancy

1.3.2.1 Guideline recommendation

Substantial variation exists in both national and international guidelines regarding clinical follow-up after hypertensive disorders of pregnancy and recommendations for cardiovascular disease prevention and screening (163, 164). Guideline development and consistency is somewhat limited by a lack of research to direct evidence-based recommendations. Additionally, study of cost-effective follow-up strategies is lacking. While most guidelines recommend postpartum follow-up to ensure resolution of hypertension and proteinuria, many do not specify a timeframe or with whom follow-up should occur. There is also substantial variation in recommendations concerning postpartum lifestyle modification and long term screening of cardiovascular health.

Within Australia, the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) recommend review by 6 weeks postpartum to determine resolution of pregnancy-related changes and referral for further management if persisting. Additional recommendations are suggested regarding lifestyle modification and counselling for

future risk of cardiovascular disease and risk of recurrence in subsequent pregnancies (165).

Although not a guideline, a position statement from the Royal Australian College of General Practitioners specifies that women should receive ongoing management from their general practitioner for medical problems arising in pregnancy such as hypertension and diabetes. It is also specifies that clinical review of maternal health should occur at 5-10 days postpartum and again at 6 weeks postpartum (166).

1.3.2.2 Strategies for postpartum follow-up

The importance of follow-up after hypertensive disorders of pregnancy is well-recognised to ensure resolution of abnormalities and provide ongoing management. In uncomplicated pregnancies, the majority of postpartum women attend a general practitioner for routine follow-up. Routine follow-up at 6-weeks may also occur with an obstetrician for women receiving private healthcare or in international models of care. For women experiencing severe morbidity related to hypertension in pregnancy such as admission to intensive care, specialist follow-up with either an obstetrician or physician is generally advised. Women with hypertension in pregnancy and minimal morbidity may be referred to their general practitioner.

In recognition of the window of opportunity the postpartum period may provide for disease and risk factor management, a number of specialised postpartum clinics and guided interventional programs have been developed and implemented worldwide. These clinics and programs offer comprehensive assessment, education and management of important lifestyle and cardiovascular risk factors to postpartum women after hypertension in pregnancy. While many women attending these clinics are reported to be highly motivated to make positive changes, participation rates are generally poor and attrition throughout programs is high (167-172). Findings of generally poor attendance at specialised postpartum clinics for preeclampsia are noted worldwide (169, 171). Reasons for poor attendance at specialist preeclampsia clinics are not well characterised, however factors linked to poor follow-up in routine postpartum care are

socioeconomic disparity, young age, lower education and fewer social supports (173, 174).

1.3.3 Chronic hypertension and pregnancy outcomes

Chronic maternal hypertension is associated with adverse maternal and perinatal outcomes, and affects around 0.6% of pregnancies in Australia although this is likely to be an underestimation (46, 48, 175). Pregnancies complicated by chronic maternal hypertension have elevated risk of superimposed preeclampsia, preterm birth, Caesarean section, and fetal growth restriction (47, 176, 177). The pooled incidence of superimposed preeclampsia from a large meta-analysis was 25.9% which is significantly higher than background rates among normotensive women of 3 - 5% (178).

Internationally, the incidence of chronic maternal hypertension in pregnancy seems to be increasing. In the United States, rates have doubled over the last decade to an estimated prevalence of 2% (47, 179). Proposed contributing factors to this include increasing average age and body mass index of women giving birth internationally.

Chronic hypertension can either be essential or secondary to specific medical conditions such as renal or endocrine disorders. Hypertension often coexists with other maternal risk factors for pregnancy morbidity such as obesity and chronic kidney disease. Importantly, cofactors such as obesity may be potentially modifiable to improve blood pressure and overall health.

Management considerations of chronic hypertension in pregnancy begin pre-conception as outlined in many international societal guidelines (83, 165). Optimisation of blood pressure control with pregnancy-safe antihypertensives and management of any coexisting conditions such as obesity and renal disease is advisable. Pre-conception counselling should include discussion regarding pregnancy risks, a plan for blood pressure monitoring and management in early pregnancy, and discussion regarding aspirin or other therapies to reduce preeclampsia risk.

1.4 THESIS HYPOTHESIS AND AIMS

Therefore, it was hypothesised that:

1. Evidence of cardiovascular risk factors and subclinical vascular changes may be detected in postpartum women after hypertension in pregnancy using non-invasive tests
2. Detection of risk factors or persisting vascular changes may aid in optimising future care of women affected by pregnancy hypertension, and promote avenues for further research

Aims of this thesis were to:

1. Determine prevalence of hypertension and characterise blood pressure patterns 6-12 months after hypertensive pregnancy (Chapter 3 and Chapter 4)
2. Determine prevalence of serum and urine markers of vascular dysfunction and cardiovascular risk in the same cohort (Chapter 3)
3. Explore pregnancy outcomes and risk factors for adverse outcomes in chronic maternal hypertension (Chapter 5 and Chapter 6)
4. Evaluate feasibility of community-based nurse-initiated maternal health screening to improve follow-up after hypertension and diabetes in pregnancy (Chapter 4)

Chapter 2

GENERAL METHODS

2.1 SUMMARY

The following chapter describes the clinical protocols, measurements techniques, handling and analysis of data of the studies described in this thesis. General methods are described separately for prospective studies involving real-time participation (Chapters 3 and 4) and historical cohort studies (Chapters 5 and 6).

2.2 GOVERNANCE

2.2.1 Ethics approval

All studies included within this thesis obtained full ethics review and approval prior to commencement by the Human Research and Ethics Committee, Eastern Health. All study documents, including patients information sheets, consent forms, study advertisement flyers and data collection sheets were approved prior to use. Any required protocol amendments gained approval prior to implementation.

Chapter 3: NASCENT Study: E21/1213

Chapter 4: Maternal Postpartum GP Follow-up Survey: LR19/001/48903

Maternal Community Cardiovascular Health Check Study: LR79/2017

Chapter 5: Pregnancy Outcomes in Chronic Maternal Hypertension Study: QA86-2017

Chapter 6: Superimposed Preeclampsia in Chronic Hypertension Study: QA66-2016

2.2.2 Collaborator approvals

Written collaborator approvals and permissions were obtained for all clinical studies involving participant recruitment and data collection in clinical settings outside of which the primary researcher had an established clinical role.

Chapter 3: Department of Obstetrics and Gynaecology, Eastern Health

Chapter 4: Department of Education and Training, Victoria: ID2018_003603

Municipal Association of Victoria

Whitehorse City Council

- Health & Family Services Department
- Immunisation Services – Environmental Health Unit

Maroondah City Council

- Health & Family Services Department

Chapter 5: Data Custodian of BOS (Birthing Outcome Systems) Obstetric Database, Eastern Health

Chapter 6: Data Custodian of BOS Obstetric Database, Eastern Health

2.3 CLINICAL DEFINITIONS

Definition of hypertension using office blood pressure measurement

'Office' or 'clinic' blood pressure refers to blood pressure measured in a healthcare setting by a clinician. Healthcare settings included clinic, hospital ward, or the research center, and clinicians were research personnel who were either doctors or nurses. Blood pressure measurements taken in a participants' home by research personnel as part of a study visit consultation were also considered office BP measurement. Office blood pressure was interpreted in accordance with ACC/AHA (American College of Cardiology/American Heart Association) Hypertension Guidelines 2017 as outlined below (43). For the purposes of this thesis, Stage 2 hypertension or higher was considered as clinically significant.

Table 2.1. Stages of hypertension as defined by office BP measurement

	Systolic blood pressure		Diastolic blood pressure
Normal blood pressure			
Normal	< 120 mmHg	and	< 80 mmHg
Elevated	120 – 129 mmHg	and	< 80 mmHg
Hypertension			
Stage 1 hypertension	130 – 139 mmHg	or	80 – 89 mmHg
Stage 2 hypertension	≥ 140 mmHg	or	≥ 90 mmHg

Definition of hypertension using ABPM measurement

Criteria for valid 24–hour ABPM reporting included a minimum of 21 daytime readings, and 7 nighttime readings over a 24–hour period to be able to determine average daytime and average nighttime blood pressure. Thresholds for hypertension on ABPM were interpreted in accordance with ACC/AHA Hypertension Guidelines 2017 as outlined below.

Table 2.2. Comparison of thresholds for definition of hypertension on office BP and ABPM measurements

	Office BP	Daytime average ABPM	24-hr ABPM
Normal blood pressure			
Normal BP	< 120/80 mmHg	< 120/80 mmHg	< 115/75 mmHg
Elevated BP	120/80 mmHg	120/80 mmHg	115/75 mmHg
Hypertension			
Stage 1 hypertension	130/80 mmHg	130/80 mmHg	125/75 mmHg
Stage 2 hypertension	140/90 mmHg	135/85 mmHg	130/80 mmHg
Stage 3 hypertension	160/100 mmHg	145/90 mmHg	145/90 mmHg

Blood pressure phenotypes

Blood pressure phenotypes were determined by correlating both the office BP measurement and daytime average ABPM result, and interpreted in accordance with the ACC/AHA Guidelines 2017. 'Hypertension' in the table below refers to Stage 2 hypertension.

Table 2.3. Blood pressure phenotypes as defined by combining Office BP and ABPM measurement

	Office BP	Daytime average ABPM
Normal BP	No hypertension	No hypertension
White coat hypertension	Hypertension	No hypertension
Masked hypertension	No hypertension	Hypertension
Sustained hypertension	Hypertension	Hypertension

Circadian blood pressure profile

Circadian blood pressure variation was characterised using the average daytime BP and average nighttime BP on ABPM, and defined in accordance with the ACC/AHA Guidelines 2017 as outlined below.

Table 2.4. Circadian blood pressure characterisation utilising difference between average daytime ABPM and average nighttime ABPM

	Difference between daytime average and nighttime average BP
Normal dipping	> 10% nocturnal BP drop
Extreme dipping	> 20% nocturnal BP drop
Non-dipping	< 10% nocturnal BP drop
Reverse dipping	Nocturnal hypertension (nighttime average > daytime average BP)

Hypertensive disorders of pregnancy

This represents a clinical spectrum of hypertensive disorders present during pregnancy and the early postpartum period inclusive of: chronic maternal hypertension, gestational hypertension, preeclampsia, eclampsia and HELLP syndrome. ISSHP (International Society for the Study of Hypertension in Pregnancy) 2018 definitions have been used within this thesis (83).

- Chronic maternal hypertension – previous documented history or treatment for chronic hypertension outside of pregnancy, or alternatively, a blood pressure ≥ 140/90 mmHg on at least two occasions at < 20 weeks' gestation of pregnancy
- Gestational hypertension – de novo maternal hypertension ≥ 140/90 after 20 weeks' gestation which subsides within 3 months of delivery
- Preeclampsia – hypertension ≥ 140/90 mmHg with evidence of proteinuria ≥ 0.03 g/mmol on urine protein: creatinine ratio, or 300mg in 24 hours, occurring after 20 weeks' gestation. Preeclampsia also includes HELLP syndrome and eclampsia
- Superimposed preeclampsia - development of proteinuria ≥ 0.03 g/mmol on urine protein: creatinine ratio, or 300mg in 24 hours, with (uncontrolled) hypertension ≥ 140/90 mmHg in women with known chronic hypertension,

occurring after 20 weeks' gestation. 'Uncontrolled' hypertension implies a rise in blood pressure which was previously controlled in pregnancy, either with or without pharmacotherapy and allowing for routine dose adjustments expected with the normal physiological blood pressure changes throughout gestation.

- Preeclampsia with severe features – development of preeclampsia with concurrent eclampsia, HELLP syndrome, severe uncontrolled hypertension or major organ failure

It is important to highlight that the current ISSHP *clinical definition* for preeclampsia does not require the presence of proteinuria for diagnosis. However, for this thesis the *research definition* inclusive of proteinuria has been used to improve generalisability to other published works, and to maintain consistent diagnostic specificity throughout clinical eras in which clinical definitions have evolved.

Secondary hypertension and essential hypertension

Secondary hypertension was included as a clinical entity in Chapter 6. Secondary hypertension was considered to be present if there was evidence of any of the following: renal artery stenosis, chronic kidney disease, hyperaldosteronism, Cushing syndrome, obstructive sleep apnoea, coarctation of the aorta, or phaeochromocytoma.

Secondary hypertension was determined not to be present (thus indicating essential hypertension) in women with chronic hypertension when they had undergone reasonable investigation for underlying secondary causes, specifically evaluation for renal disease and hormonal causes of hypertension. Evaluation for sleep apnoea and aorta coarctation were not deemed essential unless additional clinical risk factors were present. Women without a documented secondary hypertension screen were treated as missing data and omitted from specific analyses involving secondary hypertension.

Renal disease

'Renal disease' is referred to as ether an exclusion criteria (Chapter 3), or as a specific maternal characteristic of interest (Chapter 5 and 6). 'Renal disease' refers to CKD

(Chronic Kidney Disease) stage I-V as per the KDIGO (Kidney Disease Improving Global Outcomes) 2013 definition which requires the presence of structural or functional abnormalities of the kidney persisting for greater than 3 months' duration (180). These structural and functional abnormalities include any of: an eGFR < 90 ml/min/1.73m^2, persistent haematuria, persistent albuminuria > 30mg/day, or significant structural renal abnormality detected on histology or imaging.

Gestational diabetes

Gestational diabetes (GDM) was either determined from review of medical records or by self-reporting by study participants. Local clinical guidelines for the diagnosis of gestational diabetes are highly standardised and homogenous, and follow ADIPS Consensus Statement 2017 (181). GDM is confirmed by antenatal detection of the following: a fasting plasma glucose ≥ 5.1 mmol/L, or either a 1-hour glucose ≥ 10.0 mmol/L or 2-hour glucose ≥ 8.5 mmol/L following a 75g oral glucose load.

Obesity

Obesity was defined as a body mass index ≥ 30 kg/m^2 in accordance with international WHO (World Health Organisation) guidelines. Body mass index was calculated by height and weight measurement (182).

Primary postpartum haemorrhage

Definitions of primary PPH (postpartum haemorrhage) are defined by birth mode and the volume of estimated blood loss in the first 24 hours after birth. For vaginal deliveries (normal or assisted), this pertains to > 500 mL in 24 hours. For Caesaran section delivery, this is > 750 mL in 24 hours. Severe PPH is defined by > 1,000 mL blood loss in 24 hours (183, 184).

Small for gestational age

This is defined as a birthweight less than the 10th percentile, specific for baby sex and gestation at birth. The published Australia birth percentiles were used to determine 10th percentile thresholds (185).

2.4 PROSPECTIVE COHORT STUDIES

2.4.1 Study design

Chapter 3: NASCENT Study

This was a cohort study with a primary aim to determine the postpartum prevalence of hypertension on office BP measurement in women who had experienced hypertensive disorders of pregnancy. To evaluate this, a cross section of postpartum women who experienced either normotensive or hypertensive pregnancy were assessed at 6 – 12 months postpartum for various traditional and novel markers of cardiovascular risk.

Sample size estimation was undertaken to guide target participant numbers based on the primary outcome. Population prevalence of hypertension in women of child-bearing age has been estimated to be 4 - 5%, and prevalence in women with a history of hypertensive disorder of pregnancy is up to 30% (1, 4). Based on 80% power, an alpha of 0.05 and an equal enrolment ratio, target minimum sample size was n = 70. As it was anticipated a higher proportion of participants with hypertension in pregnancy may enrol, additional power calculation for an enrolment ratio of 1:2 determined a minimum sample size of n = 84.

Chapter 4: Maternal Community Cardiovascular Health Check Study

This was a population-based prospective cohort study with the primary aim to determine the prevalence of hypertension. To achieve this, a targeted maternal health screen which included measurement of blood pressure was offered to mothers accompanying their children to maternal and child health visits. Two participant groups

were involved in this study; the maternal and child health nurses who performed the health screen and the mother who received the health screen.

Minimum sample size estimation for participating mothers was calculated to be n = 456. This was based on the assumed background population prevalence of chronic hypertension in women of child-bearing age of 4 - 5%, and a 95% confidence interval of 3 – 7% (precision 2%).

Additional aims of this study were to determine the feasibility and acceptability of incorporating the maternal health check to routine maternal and child health visits. This was evaluated utilising a mixed methods design. This included capturing data on all eligible visits including reasons for not completing the health screen, in addition to time taken to complete the screen. Participating MCH (Maternal and Child Health) nurses completed a voluntary survey at the end of the study. This survey included 6 questions evaluating their perceptions and experiences from participating using a 5-point Likert scale. Additional qualitative feedback was obtained through open-ended survey questions, a guided interview with nurse team-leaders, and large-scale group discussion.

2.4.2 Study Participants

Participants included both volunteer women of childbearing (age 18 - 45 years) whom had delivered a baby in the preceding 12 months, and maternal and child health nurses seeing clients at either Whitehorse or Maroondah City Councils.

2.4.3 Recruitment

Postpartum women

Participants were approached by either the primary researcher or their maternal and child health nurse in a clinical setting in which they themselves or their infants were receiving routine care, and invited to participate in a study. These clinical settings included antenatal and postpartum clinics at Eastern health, the inpatient ward at Eastern Health, and Whitehorse and Maroondah Family Centers. Alternatively, participants responded to a study advertisement flyer by contacting researchers which

was either displayed in a place they received routine care, or distributed by a study participant whom had already completed the study.

Maternal and child health nurses

Maternal and child health nurses seeing eligible clients at approved locations were invited to participate in the study. Staff managers gave approval prior to individual nurse participation, and staff experiencing difficulty with timely work-flow were actively discouraged from participation as the study would add to their existing clinical duties. Nursing students were permitted to participate with appropriate supervision from a senior nurse.

2.4.4 Consent

Both written and verbal information was provided to potential participants relating to the relevant study. It was emphasised that participation was voluntary and would not impact current or future care (in the case of postpartum women), or work performance evaluation (in the case of maternal and child health nurses). Written or verbal consent was obtained prior to study participation as pre-specified in the HREC-approved protocol for each individual study. Participants with poor understanding of spoken or written English were permitted to participate with assistance from an Interpreter approved by the hospital or local council.

2.4.5 Study visit procedure

Chapter 3: NASCENT Study

The primary study visit occurred either within Box Hill Hospital, Eastern Health or at the participants' home residence. Study visits within the hospital occurred in an outpatient clinic or at the research centre with subsidised car parking. Home visits were offered to participants who were unable to attend to research centre in person, and there was no specific concern regarding practicality or safety about conducting the visit within their

home environment. Researchers conducting home visits used their own private vehicles for transportation, used portable study and safety equipment, wore their personal identification badge at all times, and regularly made contact with the research centre during the visit.

Study visits were carried out by either the primary researcher or an appropriately trained associate researcher. Participants gave written consent prior to the study visit occurring. Visits were organised via telephone or email at a convenient time for the participant, and flexible hours were offered including after-hours and weekends. Visits which coincided with participant menstruation were avoided where possible due to contamination risk of urine samples. For participants who had cancelled their initial or subsequent appointment, several attempts at rebooking and recontacting the participant over the following 3-6 months were made prior to excluding the participant from the study.

Study visits included conducting a detailed health interview, measurement of height, weight and blood pressure, collection of fresh urine and blood samples, and the fitting of an ambulatory blood pressure device. Following the visit, researchers returned to the research centre and processed and stored samples, organised creation of a hospital identification number, and stored data collection sheets securely. Ambulatory blood pressure monitors were either returned by the participant or collected from the participants' house by the researcher in the following 1-2 days.

Maternal medical records relating to the birth episode and antenatal care were reviewed to obtain detailed information on delivery and perinatal outcomes. Participants signed an appropriate medical release to facilitate obtaining this confidential information for study purposes.

Chapter 4: Maternal Community Cardiovascular Health Check Study

All participating maternal and child health nurses underwent group and/or individual training on at least two occasions covering the rationale for the study, the protocol for conducting the study, correct use of the study equipment and troubleshooting,

completion of data collection forms, and management of abnormal results. Individual staff participating in the study were able to contact the primary researcher, their manager, or an appropriate delegate for any questions or issues throughout the study.

During the study period, all participating maternal and child health nurses were requested to complete a data collection sheet for every 8-month child visit they conducted, including for consultations where a health check was not performed. Specific reasons for not completing the health check were also captured.

Health checks performed by the maternal and child health nurses included: description and rationale of the study, obtaining verbal consent, a 5-question health survey, measurement of height, weight and blood pressure, appropriate management of any abnormal results, and completion of the data collection sheet. All stationary and equipment required for the study was supplied by the research centre.

2.4.6 Sample Collection

Blood samples

Non-fasting venepuncture in the antecubital fossa of the non-dominant arm was performed using 21 gauge or 23 gauge needle and Vacutainer system. Serum and plasma samples were collected and sent to either the Box Hill Hospital central pathology lab (EDTA 4 ml x 1 and Serum gel tube 6 ml x 1), or stored and processed for later analysis within the research lab (EDTA 4 ml x 1 and Serum plain tube no gel 8ml x 1).

Urine samples

Mid-stream urine samples were collected in sterile containers by participants. 5 ml of urine was collected by pipette and sent to the Box Hill Hospital central pathology lab for processing. A further 5 ml was processed and stored for later analysis within the research lab. Samples with laboratory evidence of concurrent cystitis were discarded and collected again at a later date after resolution of the infection.

2.4.7 Pre-analytical handling and storage

Blood samples once collected were left to clot at room temperature for 60 minutes following collection. Both blood and urine samples were processed and stored within 4 hours of collection.

Plasma, serum and urine samples were prepared for frozen storage by low-speed centrifugation for 10 minutes at 2000g and stored in 4 x 0.5 - 1 ml aliquots at - 80° for later analysis. Samples were stored for up 3 years prior to analysis and repeat freeze - thaw cycles were avoided.

2.4.8 Laboratory analysis

Routine biochemical and haematological investigations were analysed within the onsite commercial laboratory (Box Hill Hospital Central Pathology Laboratory), as per standard operating procedure. As a commercial laboratory, strict quality–control measures such as calibration and validation are routinely performed to meet clinical standards. Analysis of markers not used in routine clinical care were performed using quantitative sandwich enzyme–linked immunosorbent assay (ELISA) technique with commercially–available kits. Sample preparation and assay procedure was carried out using the manufactures' published protocol. Samples were analysed in duplicate and concentration was derived by interpolation of the appropriate standard curve.

Soluble vascular endothelial growth factor - receptor 1

Also called soluble FMS–like tyrosine kinase–1 (sFlt–1) was measured in serum using the R&D Systems Human VEGF R1/Flt-1 Quantikine ELISA Kit (R&D Systems, Abingdon, UK). This is a 4.5 hour solid phase ELISA with a validated assay range of 31.1-2,000 pg/mL for serum samples. Intra-assay precision is 2.4–2.9% and inter–assay precision is 6.1-6.7% (186). Samples underwent a 4-fold dilution and a face mask was worn throughout the procedure to minimise possible saliva contamination. A 540nm wavelength correction was applied when interpreting optical density.

Soluble endoglin

Soluble endoglin (sEng) was measured in serum using the 2.5-hour RayBiotech–Human Endoglin sandwich-based ELISA Kit (RayBiotech, Norcross, Georgia, USA). Minimum detectable level by this assay is 10 pg/mL. Samples underwent a 100-fold dilution, and optical density was read at a wavelength of 450nm. Intra-assay precision is quoted as <10% and inter-assay precision <12% (187).

Serum copeptin

Copeptin was measured in serum samples using the Human Copeptin EIA kit (Phoenix Pharmaceuticals, Inc. Burlingame, California, USA). This is a 2-hour extraction-free competitive enzyme immunoassay, with an assay range of 0.12-2.79 ng/mL. Absorbance was read at 450nm. Intra-assay variation is quoted as <10% and inter-assay variation as <15% (188).

Soluble vascular adhesion molecule – 1

Serum soluble vascular adhesion molecule-1 (sVCAM-1) was measured using the Human sVCAM-1/CD106 Quantikine ELISA Kit from R&D Systems (R&D Systems, Minneapolis, Minnesota, USA). This is a 2-hour sandwich ELISA assay utilising cell-expressed recombinant human VCAM-1 with an accepted assay range for serum samples of 6.6-200 ng/mL. Inter-assay precision is reported as 5.5-7.8%, and intra-assay precision 2.3-3.6% (189). A 1:20 sample dilution was required which the manufacture notes may reduce recovery by 5% in serum samples. A 540nm wavelength correction was applied in interpreting results.

Myeloperoxidase

Plasma levels of myeloperoxidase (MPO) were determined on a subset of clinical samples using the 4.5 hour solid-assay Human Myeloperoxidase Quantikine sandwich

ELISA Kit from R&D Systems (R&D Systems, Minneapolis, Minnesota, USA). MPO was measured on a subset of subjects due to important pre-analytical factors; MPO is present in leukocyte granules and is released on exposure to activated platelets thus a delay from collection to storage can results in markedly elevated MPO concentration. For this reason, plasma collected in EDTA tubes and centrifuged/frozen within 2 hours of collection were analysed, as this timeframe has been shown to result in <10% increase in MPO concentration (190). Assay range is reported as 0.2-10 ng/mL with 95% recovery in plasma. Intra-assay precision is reported as 1.8-3.4%, and inter-assay precision is 8-10.8% (191). A face mask was worn throughout the assay procedure to reduce possible saliva contamination. A 540nm wavelength correction was applied in interpreting the results.

2.4.9 Blood pressure measurement

Peripheral office blood pressure measurement protocol

Chapter 3: NASCENT Study

Office peripheral blood pressure measurement was made using one of two oscillometric devices, the Oscar 2 Classic ABPM (SunTech Medical, Inc. Morrisville, North Carolina, USA) device or the Welch Allyn Spot Vital Signs® (Welch Allyn, Inc. Skaneateles Falls, New York, USA) which have been independently and rigorously validated for use in adults (192-195). An appropriately-fitted blood pressure cuff was applied to the upper arm after removal of clothing in accordance with the manufactures' guidelines. Blood pressure was measured with the upper arm positioned so that the cuff was approximately level with the subject's heart. Participants remained in a seated position, and the mean of ≥ 2 readings was used.

Chapter 4: Maternal Community Cardiovascular Health Check Study

Office peripheral blood pressure was measured by one of two TGA-approved oscillometric devices which nurses were trained to use prior to study commencement.

These devices were the Uscom BP+ (Uscom, Sydney, Australia), and the A&D UA-767S-W (A&D Medica, Tokyo, Japan) devices. Both devices have been independently validated for use in both clinical and home settings to measure peripheral blood pressure in adults (196, 197). A total of 5 sites utilised the Uscom device and 8 sites the A&D device.

Agreement between these two device measurements was not formally evaluated. The rationale was that both devices have undergone rigorous formal validation in the population for which they were being used in this study. Additionally, there was no statistically or clinically significant variation in mean population peripheral systolic blood pressure measured between sites using different devices, and a small 6 mmHg difference in measured diastolic pressure. 114/69 ± 12.5/10.5 mmHg (Uscom device) and 113/75 ± 12.9/10.9 mmHg (A&D device) respectively.

Due to the pragmatic nature of this research design, procedure for peripheral blood pressure measurement involved a single blood pressure reading in the majority of subjects. Blood pressure was measured by maternal and child health nurses on participants while they were seated and had been resting for 5 minutes. Talking and movement during measurement was discouraged. Blood pressure was measured on the left upper arm with the subject's arm resting on a table top so that the cuff was approximately level with the subject's heart. Measurement with the Uscom device takes on average 20 - 30 seconds to position to patient and fit the appropriately sizes cuff, and 50 – 60 seconds for the device to complete the measurement sequence. Measurement with the simpler A&D device took on average 15 seconds to position the patient and fit the cuff, and 25 seconds to complete the device measurement sequence.

For women with abnormal blood pressure results, nurses were encouraged to measure the blood pressure a second time after 2 – 5 minutes to ensure consistency of results. This was not enforced however and occurred at the nurses' discretion. Repeat BP measurements were recorded in 82% of assessments in which the first reading was ≥ 140/90 mmHg. The second blood pressure measurement was used in the analysis.

24-hr ambulatory blood pressure measurement protocol

Ambulatory blood pressure measurement was undertaken using the Oscar 2 Classic ABPM (SunTech Medical, Inc. Morrisville, North Carolina, USA) device which has been independently validated (192, 193). Circumference of the participants' upper arm was measured to determine appropriate customisation of cuff-size. Brachial artery position was marked on the participants' skin to facilitate appropriate readjustment throughout the 24–hour period. Devices were worn on the non-dominant arm for a period of 24 hours and scheduled to measure blood pressure approximately every 30 minutes during the daytime (08:00 to 22:00 hours), and every 60 minutes overnight (22:00 to 08:00 hours). The devices were programed to randomly vary the scheduled readings by ± 5 minutes to minimise subject anticipation. A minimum of 20 valid daytime readings and 7 valid overnight readings were required for a satisfactory 24-hr ABPM test (198). In a small number of ABPMs tests, the daytime component was satisfactory but not the overnight component. For these participants, the blood pressure phenotype was still able to be determined using the average awake BP and office BP, but not the night bloods pressure patters. Participants were required to complete an activity and sleep diary on the day they wore the ABPM device. A short survey on tolerability of the device was also undertaken, and involved identifying poor sleep quality and willingness of the participant to undergo the test again in the future. 'Poor sleep quality' was defined as per Viera et al. which included either of the participant being unable to fall asleep or being woken 5 or more times overnight due to inflation of the cuff (125).

On return of the device, data output was uploaded to the software program AccuWin Pro™ v3.4 (SunTech Medical, Inc. Morrisville, North Carolina, USA) ready for clinician interpretation.

2.4.10 Feedback of results and handling of abnormal results

Postpartum women

All participants requested and obtained an electronic or paper copy of their results after study participation. This was accompanied by a verbal or written description of the

findings, including any abnormal results by the primary researcher. Advice was given to the participant as to how to further manage any abnormal results. This included informal advice if in the field of the researchers' expertise, and/or facilitation of formal follow-up with a General Practitioner or other specialist service in the form of a written letter sent via email or post. If requested by the participant, sources of publically-available health educational material were also forwarded to the participant, for example, education on lifestyle interventions for the treatment of hypertension.

Maternal and Child Health Nurses

Maternal and child health nurses were responsible for identifying and referring on participants with abnormal findings during maternal health screening. Clear guidelines on whom and when to refer, in addition to a referral template letter were provided in the study documents. A formal data safety process was in place; the primary researcher performed regular scheduled auditing of the appropriateness of timely on-referral in real-time to ensure participant safety. Safety data on the reliability and consistency of appropriate on-referral was obtained as part of feasibility analysis. Final results of the study were presented and discussed with participating maternal and child health nurses at team meetings and group educational sessions.

2.4.11 Survey and qualitative data collection

All participating maternal and child health nurses were invited to complete an anonymous survey at the conclusion of the study. This survey included 6 questions relating to the nurses' perceptions and experiences with participating in the study. Surveys had graded responses based on a 5-point Likert scale. An additional 3 open-ended questions allowed for detailed qualitative responses. Further to this a semi-structured interview with MCH Team Leaders and a guided group-discussion with participating MCH nurses were carried out. Discussion were recorded and transcribed, then grouped by various key-themes. Qualitative data was integrated with quantitative

data findings using a triangulation framework for analysing mixed methods research findings to identify key meta-themes (199, 200).

2.5 HISTORICAL COHORT STUDIES

2.5.1 Study design

Chapter 5: Pregnancy Outcomes in Chronic Maternal Hypertension Study

This study comprised of a matched historical cohort design, aiming to determine the risk of adverse maternal and perinatal outcomes in women with chronic hypertension using a database of 43,910 deliveries. Delivery records for women affected by chronic maternal hypertension were matched in a ratio on 1: 4 with women who experienced normotensive pregnancy. After matching, case selection was determined by random number generation. Rationale for a matched cohort design was twofold; firstly, a limitation of the dataset used is the high rate of erroneous inputs for certain antenatal variables from birth years 2008 – 2012, and a smaller sample allows for more manageable manual data cleansing. Secondly, chronic maternal hypertension was rare at 0.52% prevalence, and matching may reduce potential confounding from important pregnancy - related factors which are independent of chronic hypertension, but known to strongly impact pregnancy outcome. These include: era (month of delivery) - as practice patterns may have changed over the past decade, pleurality – as twin versus singleton deliveries have differing pregnancy risks, and parity – as primiparous versus multiparous deliveries confer differing pregnancy risk. The ratio of 1: 4 was chosen as it is generally accepted in scientific literature that statistical power is minimally increased by pursuing ratios greater than 1: 4. Major fetal anomalies or congenital defects were also excluded as these are known to greatly impact birth outcome, and in particular neonatal outcome.

Chapter 6: Superimposed Preeclampsia in Chronic Hypertension Study

This was a historical cohort study aiming to determine early-pregnancy clinical risk factors associated with the development of superimposed preeclampsia in women with

chronic hypertension. Chronic hypertension was relatively rare, and affected 233 of 45,510 births (0.52%). Although a larger sample size would increase the validity of results, this was not possible due to both the rarity of chronic hypertension, and the lengthy and detailed access required for thorough medical record review necessary for this analysis.

2.5.2 Databases and data collection

Both Chapters 5 and 6 utilise obstetric medical records from two centers (Box Hill Hospital and Angliss Hospital) in Melbourne, Victoria who combined have on average 5,000 deliveries per annum. Data on 43,910 deliveries between 2008 and 2018 were available for analysis. Since July 2008, obstetric outcome data and antenatal medical records have been maintained in the Birth Outcome Systems (BOS) electronic database. This clinician-entered database routinely exports birth outcome data to the Victoria Perinatal Data Collection (VPDC), a state-government managed database overseen by the Council on Obstetric and Paediatric Mortality and Morbidity (CCOPMM). Timely and accurate reporting of birth outcome data to the VPDC by healthcare providers is mandated by the Victoria Department of Health and Human Services on behalf of CCOPMM. Accuracy of this dataset has been independently validated and published, and acknowledges very high accuracy in the domains of intrapartum and maternal characteristics, however only moderately accuracy in the domains of antenatal and neonatal items (175). Limitations of these databases are discussed in more detail in Chapter 5.

In acknowledgement of the limitations of the BOS database, a number of other sources of health information were utilised to ensure accurate capture of cases relating to the specific antenatal item: chronic maternal hypertension. Additional methods included: manual review of paper and electronic medical records, audit of clinic bookings, and review of hospital administrative coding data were utilised. Medical records were reviewed on all cases with specific ICD-10-AM diagnostic codes inclusive of: O10-O16 and I10–I15 (184). Table 2.5 and Table 2.6 below outline the accuracy of BOS in relation

to identification of chronic maternal hypertension. All datasets once created, were anonymised and stored securely on the hospital server.

Table 2.5. Actual versus BOS-classified records with chronic maternal hypertension

	Actual chronic hypertension	No chronic hypertension	Total
BOS: chronic hypertension	143	22	165
BOS: no chronic hypertension	87	43,658	43,745
Total	230	43,680	43,910

Table 2.6. Sensitivity and specificity of chronic maternal hypertension classification in BOS

	Percentage, 95 % CI
Chronic maternal hypertension classification (BOS Database) accuracy	
Sensitivity	61.4 % (44.9 – 84.1)
Specificity	99.9 % (98.9 – 99.9)

Chapter 5: Pregnancy Outcomes in Chronic Maternal Hypertension Study

Birth records from women with chronic hypertension (n = 230) were identified as outlined above from multiple sources (the BOS database, audit of clinic bookings, and hospital administrative coding data) due to the poor sensitivity of BOS for the identification of this data item. Chronic hypertension was defined as described previously in the ISSHP guidelines. All potential cases of chronic hypertension were reviewed by two reviewers. Inter-rater reliability was assessed on 95% of possible case files for agreement between reviewers regarding the identification of chronic hypertension. The second reviewer was blinded to pregnancy outcome to reduce potential subconscious bias when assessing for chronic hypertension. Kappa analysis was 0.96 indicating very good agreement between reviewers for the presence of chronic maternal hypertension.

Additional maternal demographics, baseline characteristics and all pregnancy outcome data were solely retrieved from the BOS database due to the high accuracy of BOS for intrapartum and perinatal data items. There was no additional medical record review.

Chapter 6: Superimposed Preeclampsia in Chronic Hypertension Study

The cohort of women with chronic hypertension identified for the above study was also used for this analysis. An additional 3 birth records were included in this analysis as these women delivered outside of Eastern health, and while their birth records were not retrievable from BOS, they were able to be manually added to the dataset after obtainment from their maternity unit.

Due to the nature of this study, detailed manual medical records review of all (n = 233) cases was carried out by two reviewers. Medical records were either archived paper records, scanned and electronically-stored paper records, or electronic medical records. 7 % of archived paper records requested were deemed lost and therefore unable to be reviewed. Data was retrieved using a standardised data collection sheet to minimise error. As outlined above, 95% of available records were reviewed by both reviewers to assess agreement on the two key outcome variables: chronic maternal hypertension and preeclampsia. Kappa analysis was 0.96 for chronic hypertension and 0.94 for preeclampsia, indicating very good agreement.

2.6 DATA STORGAE AND HANDLING

Data from both historical and prospective studies was stored and handled in a way to maintain participant privacy and anonymity. Unique patient identifiers were removed from all medical records and databases wherever possible, or changed to numerical code which could be traced using a code key if required in the event of potential safety concerns. Some paper data collection sheets and medical records were not able to be de-identified, and were stored securely in a locked cupboard or office at the research center at Box Hill Hospital. Electronic databases were stored on the secure hospital server.

2.7 STATISTICAL ANALYSIS

Descriptive and analytical statistics were used for all studies. Groups were described using frequency (with percentage), median and inter-quartile range (non-parametric distribution), or mean ± standard deviation. Comparison between two groups was performed using the chi-square test for categorical variables, and the Mann-Whitney U-test or unpaired t-test for non-parametric or parametric variables respectively. Distribution normality was determined by visual inspection of data distribution histograms. Comparison between three groups was carried out using chi-square test for categorical variables, and the Kruskal-Wallis or one-way ANOVA tests for non-parametric and parametric variables respectively. Associations between outcomes and various exposure risks were determined using univariable and multivariable logistic regression. Adjustment covariates were chosen either due to statistical significance on univariable analysis, or due to either biological plausibility or known association from other published literatures. Care was taken to ensure mutually exclusive data points were handled appropriately in analyses. For example, primiparous women were not eligible to have a past history of hypertension in pregnancy, and women with type 1 diabetes were not eligible to have gestational diabetes. Statistical significance was set at $p < 0.05$ (two-sided). Population attributable fraction was applied as described by Leviton 1973 et al. to determine the contribution of a specific risk factor or exposure to an outcome if interest in the study population (201). Qualitative data underwent descriptive analysis with identification and exploration of key themes, then analysis for thematic convergence with quantitative findings using a triangulation framework. All analyses were performed using STATA 15.0 (StataCorp, College Station, Texas, USA). Figures were prepared using STATA 15.0 or GraphPad Prism 5.0 (GraphPad Prism Software Inc. San Diego, California, USA).

Chapter 3

THE NASCENT STUDY

3.1 ABSTRACT

Background: The observed association between hypertensive disorders of pregnancy and increased long-term maternal cardiovascular risk remains poorly understood. This study aims to evaluate women after hypertension in pregnancy for evidence of subclinical endothelial dysfunction, and for hypertensive and circadian blood pressure abnormalities.

Methods: In this cross-sectional study, 88 postpartum women who experienced either a normotensive pregnancy (NP), gestational hypertension (GH) or preeclampsia (PE) were evaluated. Women with known chronic hypertension or renal disease were excluded. Assessments occurred at 6-12 months postpartum, and included office BP and 24-hr ambulatory BP measurement (ABPM), serum creatinine/eGFR, serum sVCAM-1, sEng, sFlt-1, MPO, uric acid and urine protein estimation. Women were surveyed on their follow-up after hypertensive pregnancy.

Results: Stage 2 hypertension was highly prevalent (29.8%) after hypertensive pregnancy (GH or PE) on office BP measurement. Hypertensive phenotypes on ABPM were also more prevalent after hypertensive pregnancy: masked hypertension was present in 28.6% of GH, 31.4% of PE and 9.1% of NP, p= 0.002. An office BP > 130/80 mmHg was a strong predictor of masked hypertension after hypertensive pregnancy, OR 13.1 (95%CI 2.2-59.7). Sustained HT was present in 50.0% of GH, 17.1% of PE, and 9.1% of NP, p= 0.008. Women with PE had the highest rates of nocturnal non-dipping phenotype, although this did not reach statistical significance (42.4% for PE group vs 36.0% for GH and 23.7% for NP). 42.8% of women in the GH group and 12.13% of women with PE were taking antihypertensives during the study. There was no significant difference between groups in renal function or markers of endothelial dysfunction. A significant proportion of women reported no formal medical follow-up after hypertensive pregnancy.

Conclusion: Sustained HT, masked HT and nocturnal non-dipping phenotype were frequently observed in women after hypertensive pregnancy using ABPM. An office BP threshold of >130/80 mmHg may help determine who would benefit from ABPM testing. Given the associations between both masked HT and nocturnal non-dipping with long

term cardiovascular risk, routine ABPM should be considered in the postpartum follow-up after PE or GH. Postpartum evaluation of blood pressure after hypertensive pregnancy has room for improvement.

3.2 INTRODUCTION

Extensive high quality observational data shows a strong association between hypertensive disorders of pregnancy and increased long term cardiovascular risk in women. These include risks such as cardiac disease, hypertension, stroke and chronic kidney disease, and persist after adjustment for other potential coexisting risks such as smoking, diabetes or elevated body mass index (2, 155). It remains unclear as to whether this association is due to shared risk factors and genetic predisposition which lead to a lower threshold for developing clinical cardiovascular disease, or whether a preeclamptic episode independently contributes to persisting vascular dysfunction, thus also predisposing to premature cardiovascular disease. In recognition of this, a history of hypertension in pregnancy is now increasingly identified as an important factor in the risk assessment and prediction of future cardiovascular disease in women (84).

Initial investigation into the pathogenesis of cardiovascular disease in women with a history of preeclampsia has revealed evidence of hypertension and persisting endothelial dysfunction, both hallmarks of the preeclamptic syndrome in a proportion of women in the months and years following pregnancy. A major limitation of studies thus far is the wide variation in the time-point of assessment after birth, small sample size, and lack of longitudinal data to understand the natural history of subclinical cardiovascular abnormalities in this population with more clarity.

A number of emerging tools to aid in the prediction of cardiovascular risk are increasingly acknowledged for their improved sensitivity and specificity in comparison to existing traditional risk factor assessment. Ambulatory blood pressure monitoring is one such tool, and has been shown to provide additional accuracy in predicting cardiovascular outcomes over office blood pressure measurement (43). ABPM has the ability to characterise circadian blood pressure changes and determine the presence of masked hypertension or other abnormalities which may not be detected by routine office BP measurement. It has been observed that women in pregnancy destined to develop preeclampsia show blunted or absent nocturnal blood pressure dipping before the onset of overt hypertension (202-204). Two recent studies have investigated ABPM in the first year postpartum to evaluate for the persistence of these changes after birth.

Although high rates of both hypertensive and nocturnal dipping pattern abnormalities were observed, certain crucial limitations are worth noting; specifically an absence of healthy control group for comparison, and the use of ABPM in the early postpartum period when sleep patterns are highly disrupted which is known to significantly affect circadian blood pressure patterns (159, 205).

There is increasing interest to discover specific biomarkers to both accurately predict and diagnose subclinical cardiovascular disease in various at-risk populations. Many of the biomarkers demonstrated to be of potential relevance in cardiovascular disease prediction have also been implicated in the pathogenesis or diagnosis of preeclampsia. Despite this, little is known about the postpartum persistence or resolution of these biomarkers. Some of these makers are closely related to endothelial dysfunction and activation such as VCAM or soluble Flt-1, and others such as serum copeptin, are markers of physiological stress and neurohormonal activation.

This study aims to further characterise the persistence or resolution of subclinical vascular changes in women after pregnancy complicated by a hypertensive disorder in the first year after birth. Evaluation of vascular changes will utilise non-invasive tests to assess both traditional and novel markers of vascular risk. Furthering the understanding of postpartum changes may both promote future avenues for research, and help guide optimisation of care in women after hypertension in pregnancy to modify future health risks.

3.3 METHODS

Women with a history of either hypertensive or normotensive singleton pregnancy were enrolled to participate in an observational study at 6 -12 months postpartum between 2014-2018. ISSHP 2018 definitions for both preeclampsia and gestational hypertension were used, and included the requirement for hypertension and proteinuria > 0.3 g/mmol to be present for the diagnosis of preeclampsia. Women were required to give written consent, and those with pre-existing chronic hypertension, renal disease, or current pregnancy were excluded. A number of participants were taking antihypertensives at

the time of study inclusion, however this did not preclude participation as they were not known to have hypertension prior to pregnancy.

Baseline demographics, medical history, pregnancy complications and outcomes were recorded at the main study visit. Samples and measurements were collected and included: height and weight measurement, office BP and ABPM measurement, blood collection for: creatinine, liver function tests, uric acid, serum and plasma for storage, and urine collection for: microscopy and dipstick, albumin/creatinine ratio and protein/creatinine ratio. Routine biochemical investigations were performed in the onsite commercial laboratory. Estimated glomerular filtration rate (eGFR) was derived from the CKD-EPI formula using serum creatinine. Markers of endothelial dysfunction and activation (VCAM-1, sEng, sFlt-1, MPO) and neurohormonal activation (copeptin) were measured by commercially-available ELISA.

Ambulatory blood pressure was also measured for a 24-hr period in consenting participants using an appropriately fitting cuff. Participants were asked to continue their regular activities, record a sleep diary, and submit a short survey on device tolerability.

The primary outcome to determine the prevalence of office hypertension (thus 'uncontrolled' hypertension) was a comparison between two groups; normotensive pregnancy and hypertensive pregnancy. It was clear however that within the hypertensive pregnancy group there were distinct differences between the subgroups of GH and PE in relation to baseline characteristics and pregnancy outcomes. For this reason, all secondary outcomes were evaluated as a comparison between three groups; normotensive pregnancy, gestational hypertension and preeclampsia.

Evaluation of factors influencing follow-up of women after hypertension in pregnancy involved both analysis of medical discharge summary coding accuracy for pregnancy hypertension diagnosis, and survey of women on their medical follow-up after hypertensive pregnancy.

3.4 RESULTS

A total of 88 women completed the study at a median of 8.4 ± 2.5 months postpartum. There were 31 participants with normotensive pregnancy, 17 with gestational hypertension, and 40 with preeclampsia. Whilst it was intended to include an even distribution of normotensive (NP) to hypertensive pregnancy (GH and PE) participants, women with normotensive pregnancy were particularly difficult to recruit, and the final ratio was 1:2 (Figure 3.1). Additionally, a number of women were mislabelled as PE or GH on their medical record, and so switched diagnostic categories after study enrolment. This is discussed and explored further in section 3.4.5.

3.4.1 *Baseline characteristics and pregnancy outcomes*

There were a number of differences between groups in relation to baseline characteristics (Table 3.1). Women in the PE group were more likely to be nulliparous and have a past history of hypertension in pregnancy. Women in the GH group were more likely to have a higher BMI or be obese.

In relation to pregnancy outcomes, there were a number of differences between groups to note. In particular, women with hypertension were more likely to have delivery induced and experience postpartum haemorrhage. Women with hypertension were also more likely to be readmitted after hospital discharge, and need of intensive care during their birth episode (Table 3.2). Neonatal outcomes were also differing between groups, with a statistically significant but perhaps not clinically significant difference in gestation at delivery, with all groups having a median gestation > 38 weeks. There was a higher proportion of preterm delivery, small for gestational age and nursery admission in the preeclampsia cohort.

3.4.2 *Blood pressure evaluation*

Office blood pressure was compared between those with normotensive pregnancy and those with hypertensive pregnancy. Stage 2 hypertension was present in 29.8% of

women after hypertensive pregnancy on office BP measurement, with mean BP being 121/73 mmHg in the normotensive pregnancy group and 132/80 mmHg in the hypertensive preganncy group (Table 3.3).

Given the differences in baseline characteristics between women with preeclampsia and gestational hypertension, office blood pressure was also evaluated in these two subgroups compared to normotensive pregnancy (Table 3.4 and Figure 3.2). Mean office blood pressure was significantly different between groups. A higher proportion of women in both the gestational hypertension and preeclampsia cohorts had stage 1 or stage 2 hypertension as compared to the normotensive pregnancy cohort, p=0.001.

Ambulatory blood pressure testing was successfully completed in 85% of study participants (Table 3.5). Women with gestational hypertension reported poorer tolerability of ABPM compared to other groups; reduced sleep quality was more frequently reported and less women would be happy to undergo the test again for research or medical indications compared to other groups. Significant differences in both systolic and diastolic 24-hour average blood pressure were observed between groups. These significant differences were also observed across groups in both the daytime average and nighttime average blood pressures.

By combining the office blood pressure and daytime average blood pressure, the blood pressure phenotype was determined. A statistically significant difference between groups is observed across blood pressure phenotypes and use of antihypertensive therapy (Table 3.6). Women after gestational hypertension or preeclampsia were frequently observed to have the undesirable blood pressure phenotypes of masked or sustained hypertension. The relative proportion of undesirable blood pressure phenotype by pregnancy category and antihypertensive use is visually appreciated in Figure 3.3 and Figure 3.4. As blood pressure phenotype is determined by systolic blood pressure only, the spread between pregnancy groups and blood pressure phenotype of both systolic and diastolic blood pressure is appreciated in Figure 3.5.

The relationship between office blood pressure category and masked hypertension were explored in more detail. In women with a history of hypertensive pregnancy, Stage 1

hypertension on office blood pressure measurement was a strong predictor of masked hypertension with an odds ratio of 13.1 (95% CI 2.89-59.7) (Table 3.7).

Nocturnal blood pressure patterns were also assessed by determining the ratio of daytime average blood pressure to nighttime average blood pressure. A higher proportion of non-dipping patterns were observed after hypertensive pregnancy compared to normotensive pregnancy, although this did not reach statistical significance (Table 3.8). The relative proportion of non-dipping phenotype per pregnancy category is seen in Figure 3.6.

3.4.3 *Biomarker evaluation*

The main observation in biomarker evaluation was that uric acid was statistically different between groups, with the highest in the GH group, followed by the PE group (Table 3.9). Additionally, there is a trend towards reduced eGFR in the GH group however this did not reach statistical significance. There was no significant difference between groups in other markers of endothelial dysfunction and neurohormonal activation.

3.4.4 Evaluation of medical record specificity for HDP

It was observed throughout data collection that the hospital medical records regarding delivery (birth episode discharge summary) did not reliably reflect the correct pregnancy blood pressure category diagnosis. The discharge summary classification and actual pregnancy blood pressure diagnosis were compared and significant variability across all pregnancy categories was observed (Table 3.10). The sensitivity and specificity of the discharge summary accuracy for hypertension in pregnancy was evaluated (Table 3.11). Discharge summary accuracy for preeclampsia had a sensitivity of 60.0% (95%CI 43.3–75.1) and specificity of 91.7% (95%CI 80.0–97.7). Gestational hyertension discharge summary diagnosis had a sensitivity of 62.5% (95%CI 35.4–84.8) and specificity of 80.3% (95%CI 68.6–89.1). Any hypertensive disorder of pregnancy (either gestational

hypertension or preeclampsia) on dicharge summary performed better with a sensitivity of 85.9% (95%CI 73.8–93.6).

3.4.5 Evaluation of follow-up care pathways after HDP

Study participants who experienced hypertension in pregnancy were also surveyed on their medical follow-up after delivery. The survey involved questioning if they had received a medical check with a doctor which included a blood pressure check prior to study participation. 32.5% of women after preeclampsia and 52.9% of women after gestational hypertension reported they had not yet received a medical review which involved a blood pressure check (Table 3.12). Women who were followed-up after gestational hypertension did so at the family doctor, whereas a large proportion of women after preeclampsia were followed up by a specialist clinic.

3.5 DISCUSSION

This study aimed to comprehensively evaluate a cohort of women after hypertensive pregnancy for evidence of subclinical vascular disease. The most prominent finding was that of a high prevalence of hypertension across both the gestational hypertension and preeclampsia groups. Not only did this represent a new diagnosis of hypertension for many, but also a sign of uncontrolled hypertension as a number of participants were taking antihypertensives at the time of study participation. Additional clear findings were that follow-up after hypertensive disorders of pregnancy could be improved, and that research participation for postpartum women is difficult.

Persisting postpartum hypertension after hypertensive disorders of pregnancy is frequently reported in the literature, however quoted rates vary significantly from 9% to 45% (92, 205, 206). Studies are often limited to evaluating preeclampsia in isolation, and women with gestational hypertension are excluded from analysis. Many studies utilise registry or survey data, are of small sample size, have unclear protocols for blood pressure measurement, and are a number of years postpartum which can limit generalisability. This current study is consistent with other reports of showing increased rates of persisting sustained and masked hypertension in women after preeclampsia,

although has the benefit of both normotensive pregnancy and gestational hypertension comparator groups which is a limitation of other studies (121, 205, 207). A comparator group is vital in considering the impact of caring for an infant in the interpretation of home blood pressure and circadian blood pressure changes. Both high levels of psychosocial stress and distress, and overnight waking have been shown to elevate blood pressure and disrupt normal biological circadian rhythms in women (124).

It is important to consider whether the high rates of persisting postpartum hypertension observed represent a group of women who had undiagnosed pre-existing hypertension. Preconception blood pressure measurements were not available for this cohort, which is a limitation of the study. This however, is very common to observational studies as young women tend not to undergo routine blood pressure screening outside of pregnancy. Documentation of blood pressure measurements are often limited to pregnancy, and due to physiological gestational cardiovascular adaptions, normotension in pregnancy does not necessarily represent normotension outside of pregnancy.

In the small number of studies that have been able to measure blood pressure longitudinally from pre-gestational to postpartum, preeclampsia and large gestational weight gain have been associated with de novo chronic postpartum hypertension in previously normotensive women (208, 209). In one individual patient data meta-analysis examining risk of preeclampsia recurrence, women identified with de novo chronic hypertension after a hypertensive pregnancy episode were in the highest risk group for a recurrent hypertensive disorder in their next pregnancy (41% recurrence) (210). This observation does add weight to the importance of identifying chronic hypertension after preeclampsia or gestational hypertension. Identification will not only allow for treatment, but also for pre-conception counselling and early pregnancy risk stratification and modification in the next pregnancy.

The observed rates of postpartum hypertension in the gestational hypertension group in this study were higher than other published cohorts. The majority of women with gestational hypertension were also obese; a known cofactor and cause of elevated blood pressure in young women. To determine the prevalence of postpartum hypertension independent of coexisting obesity after gestational hypertension, a larger sample size

would be required. Even so, obesity is an important modifiable risk factor for cardio-metabolic health, and reducing weight between pregnancies is associated with more favourable pregnancy outcomes in the next pregnancy (209). It remains unknown if the main benefit of weight loss is through improvement in blood pressure and vascular health, a reduced incidence of gestational diabetes, or through other mechanisms.

Gestation hypertension is not as well studied in the postpartum period as preeclamspia, and women often receive follow-up with a family doctor rather than at a specialised clinic. It is possible that selection bias may have contributed to a higher proportion of women in this cohort who had not yet had follow-up, and so had higher rates of uncontrolled hypertension. A lack of follow-up to date may be an incentive to participate in research. In comparison, women who had received follow-up and were satisfied with their care may hypothetically be less motivated to participate in a research study, and also have better-controlled blood pressure (with antihypertensive use) than those who had not had follow-up.

An additional factor which may have contributed to higher office postpartum blood pressure in this study versus other studies is the blood pressure measurement protocol. Other published studies have utilised protocols which include the subject resting quietly in a room for 10 minutes before measurement, and an average of three measurements (211, 212). In contrast for this study, subjects were with their baby and not left alone, resting in a chair, and had a minimum of two measurements taken. Whilst this may have contributed to higher office readings, it would seem unlikely to have contributed significantly given the high rates of masked hypertension observed in this study.

Another observation worthy of comment is that there was a higher than expected rate of hypertension in the normotensive pregnancy group. Although none of these women were known to have pre-existing hypertension or a hypertensive disorder of pregnancy, an association with certain pregnancy outcomes which can be associated with chronic maternal hypertension is observed in this group. Of the four women with stage 2 office hypertension (also confirmed with ABPM), 3 had small for gestational age babies, and the remainder were obese. It is possible that these women may have had underlying chronic hypertension given the known association with obesity and low birth weight in

the literature. Of note, the Australian Institute of Health and Welfare has published rates of hypertension in women aged 20-45 based on office blood pressure screening to be 6-10%, which is higher than other reports, but in keeping with the findings of this study (1).

Masked hypertension was highly prevalent in the preeclampsia and gestational hypertension groups. This has been observed by other groups after preeclampsia, but is not as yet described after gestational hypertension in the literature. For the NASCENT cohort, masked hypertension was present in 31.4% of participants, whereas other studies have observed rates of 11.6% at 6-12 weeks postpartum, and 17.9% at 12 months postpartum (205, 207). Of note, these studies only included women with preeclampsia.

Masked hypertension has been independently associated with adverse long term cardiovascular outcomes, and in some studies, this risk is higher in comparison to sustained or office hypertension (100, 101). It is hypothesised that masked hypertension may be a sign of sympathetic overactivity. Sympathetic overactivity is a phenomenon known to contribute to a large proportion of essential hypertension in young adults, and has also been observed in high prevalence amongst women in the years after preeclampsia.

To diagnose masked hypertension, use of a 24-hour ambulatory blood pressure device is required. Whilst this device is recommended as standard-of-care to both diagnose and manage hypertension, it is still not currently subsided in Australia through the Medicare program, costing consumers between $80-$160 for testing. In addition to cost, the device is difficult to use for persons with significant obesity as cuffs are poorly-fitting and not designed to fit the taper of the upper arm often seen in young overweight women. This was observed in the NASCENT cohort whereby women with higher BMIs reported poorer quality sleep and were less likely to agree to have the test again for either research or medical purposes. It would seem that design improvements and consideration of Medicare eligibility are required to make this test more accessible to a wider range of populations who may gain benefit.

To help further direct who best to refer for ABPM given potential difficulties with cost and accessibility, stage 1 hypertension on office blood pressure management was shown to be a strong predictor of masked hypertension after hypertensive pregnancy in this study.

Abnormal circadian blood pressure patterns, and specifically higher rates of nocturnal non-dipping were observed in the preeclampsia group. This has been observed by others in both the antenatal and postpartum period (121, 202-204, 213-215). Nocturnal non-dipping and hypertension remain of prognostic value in the prediction of long term cardiovascular risk in the general population, although prognosis is currently unknown in the hypertensive pregnancy population (106, 107).

Hypothesised mechanisms for reduced blood pressure drop at night in hypertensive disorders of pregnancy include increased salt sensitivity, increased sympathetic activation, and sleep disordered breathing (216-223). Additional to this, psychosocial stressors in the general population have been shown to affect nocturnal blood pressure, and these stressors are known to be highly prevalent in the first year after preeclamptic pregnancy (224, 225). These include chronic anxiety, depression, post-traumatic stress disorder, poor sleep quality and 'stressful life circumstances' (124). Mental health and self-perceived levels of stress were not captured in the NASCENT cohort, however serum copeptin levels were measured and have been shown to correlate in other patient groups with psychological and physical stress (138, 139). No correlation between serum copeptin and nocturnal non-dipping or poor sleep quality was observed in this study. Larger participant numbers may be required to further confirm the absence of a relationship, especially when considering the other factors which may influence copeptin levels such as hydrations status and breastfeeding.

There has been question about the reproducibility of nocturnal blood pressure patterns on ambulatory blood pressure measurement, although this has been in mixed-sex and older populations (94). Reproducibility of the circadian blood pressure findings remains uncertain in young postpartum women, and may be a difficult question to answer as many women in this study cohort would not wish to undergo an additional ABPM test for either research purposes or a medical indication.

A large number of women in the hypertensive pregnancy groups were found to have untreated or uncontrolled hypertension, whereby they had either stated they had undergone follow-up including blood pressure measurement with a doctor, or they were taking antihypertensive medications at the time of study enrolment but still observed to be hypertensive. A number of possibilities may explain these observations, and include: dynamic changes in the natural history of postpartum hypertension, unclear guidelines on how to diagnose and manage hypertension in young women, and patient adherence.

The natural history of blood pressure changes month-to-month in the first year after birth have not been vigorously studied. Factors such as breastfeeding, bodyweight change, changes to diet and exercise, hormonal contraception and recurrent pregnancy are all factors which are known to affect blood pressure in women of childbearing age (38, 39, 204, 221, 226, 227). In this study, the majority of participants had discontinued regular breastfeeding by the time of study visit assessment, and use of hormonal contraception was not captured. It is possible that an individual with previously well-controlled blood pressure at 6 - 12 weeks postpartum, may have higher blood pressure at 6 - 12 months postpartum due to discontinuation of breastfeeding and recommencement of hormonal contraception. Alternatively, an individual may not have had their blood pressure follow-up up since discontinuation of antihypertensives at 6 - 12 weeks postpartum, and may still require treatment. These possibilities highlight the likely need for longitudinal care and monitoring of blood pressure after hypertensive disorders of pregnancy.

Another factor that may influence management of blood pressure in young women in Australia are the lack of clear consensus guidelines on when and how to treat hypertension. There are many challenges in cardiovascular risk assessment in young people. Conventional blood pressure thresholds for the diagnosis and treatment of hypertension are based on long term risk prediction with solid longitudinal evidence supporting this approach. However, most risk prediction tools are limited to older populations such as for post-menopausal women, with poor validity in younger populations. The Australian Heart Association Guidelines, which are very commonly used by general practitioners to guide management of hypertension, follow the approach that indication to treat blood pressure be based on high absolute

cardiovascular risk (228). This is problematic in the screening of young people as absolute risk, especially in young women, is invariably low meaning that individuals even with very abnormal risk profiles will not be recommended for treatment. Additionally, the tools used for cardiovascular risk assessment have not been validated in persons < 45 years of age. Calculation of a 'cardiovascular risk age' which focusses on relative risk, rather than absolute risk for age has been proposed as an alternative tool to guide management decisions, however still needs validation for use in young women (229).

An unexpected observation of this study was the high-rate of self-reported poor follow-up after hypertensive pregnancy, even after allowing for a degree of participant recall-bias. There are likely patient, health service, community, and system factors at play which will be explored in more detail.

Poor follow-up after hypertensive disorders of pregnancy is a recognised phenomenon in both the developed and developing world for which there are currently limited solutions (53, 167, 169, 171). Although postpartum follow-up is almost universally recommended, a lack of consistent and evidence-based guidelines for how and when to follow-up has been suggested as a possible contributing factor (164, 230).

One tool introduced by some centres to combat this are specialised postpartum clinics. These clinics are specifically designed to utilise the postpartum period as a 'window of opportunity' to modify future disease risk, optimise health prior to future pregnancy, and instil lasting healthy lifestyle behaviours. Some studies have shown that women are particularly receptive and motivated to make beneficial health modifying behaviours in the postpartum period (167, 231, 232).

Smith G et al. evaluated the introduction of one such clinic; a specialised 'Maternal Health Clinic' in Ontario, Canada, designed specifically for postpartum health maintenance and disease prevention (168). Women with pregnancy complications associated with cardiovascular or metabolic syndrome risk are referred at the time of delivery, and invited to attend the free clinic for comprehensive evaluation at 6 months postpartum. Women are sent an information and educational package and given several phone-calls over the 6 months to encourage attendance. Despite this, only 42.8% of women attended, with the remainder either not-showing or cancelling. Risk factors for

non-attendance were being younger, less educated, and having a higher BMI. This example highlights the challenges of designing a system of follow-up catering for the diverse socioeconomic, educational and cultural backgrounds of mothers. For the NASCENT cohort, although many participants were from culturally diverse backgrounds, most women had a similar education level and socioeconomic status based on residential SEIFA (Socio-Economic Indexes for Areas) score. This suggests other factors such as health system factors, in addition to patient factors may be at play in explaining the poor rates of postpartum follow-up in this cohort.

In relation to the NASCENT study cohort, factors impacting the likelihood of follow-up are worth considering from very soon after birth, prior to hospital discharge. A woman who experiences a hypertensive disorder may not have her disease appropriately recognised, fail to receive appropriate education on the diagnosis, including recommendation on management and follow-up, or have a birth discharge summary which accurately reflects the important events of birth, including a diagnosis of hypertensive disorder. The setting of a postnatal ward and timing after a complicated delivery may also not be the most appropriate setting for patient education to ensure important information is retained. Psychological and physical stress, in addition to cognitive impairment are known to affect women in the early postpartum period after preeclampsia, which may impact effectiveness of in-hospital education (233, 234).

Women will usually be referred to their specialist or family doctor for further follow-up after hypertensive pregnancy. Many factors may potentially affect attendance at this follow-up: access, cost, conflicting priorities, health literacy and education, social supports, previous positive/negative experiences with medical professionals, and a lack of symptoms leading to the presumption it is unnecessary.

In the NASCENT cohort, some women did attend follow-up with a doctor, however did not have their blood pressure checked. Although a blood pressure check is recommended for all women in the 6-week postpartum maternal health check in some guidelines, it is only recommended for those after a hypertensive disorder in other guidelines (165, 166). It is possible that an inaccurate birth summary may have led to a family doctor omitting a blood pressure check when they otherwise would have, or

omission may occur as a result of prioritising other tasks and managing symptomatic conditions when under time and resource constraints. Survey data from Australian general practitioners supports these potential factors, whereby timely birth discharge documentation is not received in a quarter of consultations, and postpartum consultations frequently take longer than expected (235, 236). Improving communication between healthcare providers and utilising opportunistic assessment of maternal health during any healthcare interaction may be possible approaches to improving follow-up, as many mothers have been shown to access health care several times in the first year postpartum, particularly for their children (237, 238).

There were no significant differences observed in biomarker levels between groups aside from serum uric acid. The study population used was of asymptomatic individuals belonging to different risk profile groups, and observing subtle differences may require a larger sample size to measure between-group differences. An additional factor may have been the sensitivity and reproducibility of the ELISA assays used, whereby some manufactures quoted > 10% inter and intra-assay variability (188). Of note, the NASCENT study included mostly term preeclampsia, and included the subpopulation of gestational hypertension leading to a more heterogeneous study population of milder disease severity. In contrast, other groups which have observed differences in postpartum endothelial markers despite a small sample size utilised enriched study populations of women with preterm preeclampsia, a marker of severe disease. To confirm trends and explore these biomarkers further, a larger and homogenous sample using more sensitive and reproducible assays may produce more reliable results.

Uric acid was observed to be highest in the gestational hypertension group followed by the preeclampsia and normotensive group. Uric acid itself is known to be elevated during the syndrome of preeclampsia, although is no longer included as a diagnostic criterion (83). It is known to return to the normal range after preeclampsia has subsided. In this study, whilst all women had serum uric acid levels within the normal range for adult females, there were clear between-group differences. Uric acid can be elevated in a number of disease and phenotypic states such as: chronic kidney disease, genetic metabolic conditions, increased cell turnover, fatty liver disease, chronic gout, obesity and hypertension. Whilst acknowledging that elevated uric acid can occur in these

conditions, it has also been demonstrated to independently predict cardiovascular events and all-cause mortality in the general population. Uric acid has both extracellular pro-oxidant and intracellular anti-oxidant effects, and can induce endothelial dysfunction and activation of the renin-angiotensin system (239, 240). The exact mechanism which links cardiovascular disease and elevated uric acid currently remains elusive. It is possible in this cohort that uric acid is elevated due to co-existing hypertension, obesity, and metabolic syndrome. However, due to the high prevalence of hypertension and obesity, an independent association is unable to be determined.

A limitation of this study is the small sample size and lack of longitudinal data despite recruitment over a number of years. A longitudinal design was initially intended for this study. However, it was clearly not feasible using available time and resources and was abandoned in favour of a cross-sectional design.

Both consideration of participation and commitment to participation once-enrolled were found to be difficult for postpartum women approached to participate in this study, particularly for women after normotensive pregnancy. This is not a unique finding, and difficulty in recruiting postpartum women for research has been observed by other researchers (241). Many factors may influence research participation, and in this study factors such as family caring commitments, personal mental health, and lack of incentive relative to effort were cited by participants as reasons for withdrawing consent. Concerted effort was made to improve accessibility and inconvenience to participants with alteration of the study design to offer flexible and out-of-hours home visits, but ultimately a large number of participants still withdrew due to social circumstances or lack of willingness.

Another potential limitation of this study is that makeup of the study population may potentially be influenced by an individuals' motivation for participation, as this may differ between cohorts and introduce bias. For example, altruism may be the main motivation for research participation in otherwise healthy women after normotensive pregnancy. Alternatively, women who have experienced preeclampsia may see participation as an investment with potential payoff; to gain a better understanding of the condition they have experienced, or undergo a medical assessment when they had

not yet undertaken formal postpartum follow-up, despite advisement to do so after delivery. Possible selection bias due to these reasons was not formally explored in this study design, however are important to consider when interpreting prevalence of pathological findings.

Generalisability of study findings to the general population is an important consideration and potential limitation. It has been acknowledged in the literature that other common and well-studied postpartum conditions such as postpartum depression limit external validity in that socioeconomic and culturally diverse populations remain understudied (242). Whilst there was some ethnic and socioeconomic diversity within this study sample, outer metropolitan and rural/regional women were underrepresented. Women giving birth in regional areas of Victoria have recently been shown to have increasing rates of obesity and adverse pregnancy outcomes (243). Whilst obesity is an important independent risk factor for hypertensive disorders of pregnancy, so too is gestational diabetes in which certain racial groups are at increased risk, even when of a healthy BMI. These are important considerations in interpreting the generalisability of research findings, and translating into healthcare policy change in the care of postpartum women.

Strategies to improve both postpartum care and research need to be carefully designed to cater to this unique population. Targeting factors contributing to an individuals' motivation rather than focussing on education alone has been shown to be more effective in improving adherence to medical care in women's cardiovascular health (12). Health behaviours of postpartum women are strongly motivated by family and their children, and often care of children is prioritised over their own health. Incorporating both maternal health review and postpartum research into routine care pathways for both mothers and their children, may be a potential strategy to improve both postpartum care and research participation. Additional to this, the inclusion of various metrics in longitudinal research designs to evaluate children's health in addition to maternal health, may also potentially incentivise maternal health research participation, and has been observed to be a successful strategy in some research designs (212, 244).

3.6 CONCLUSION

While acknowledging the limitations, this study demonstrates a number of chronic postpartum hypertensive blood pressure abnormalities across the spectrum of hypertensive disorders of pregnancy in the first year after birth. Within this study cohort, much of the chronic hypertension observed was undiagnosed or uncontrolled. In addition to this, specific factors which may impact long term management of women after hypertensive pregnancy such as accurate birth discharge summaries and timely medical follow-up were explored, and found to be lacking. Postpartum follow-up is an important opportunity to allow for early intervention given the association between chronic hypertension, and both adverse pregnancy outcomes for future pregnancies and long term cardiovascular risk. Further exploration of how best to improve follow-up and modify disease risk needs to be both a clinical and research priority.

3.6 ACKNOWLEDGEMENTS

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Figure 3.1 NASCENT study flowchart

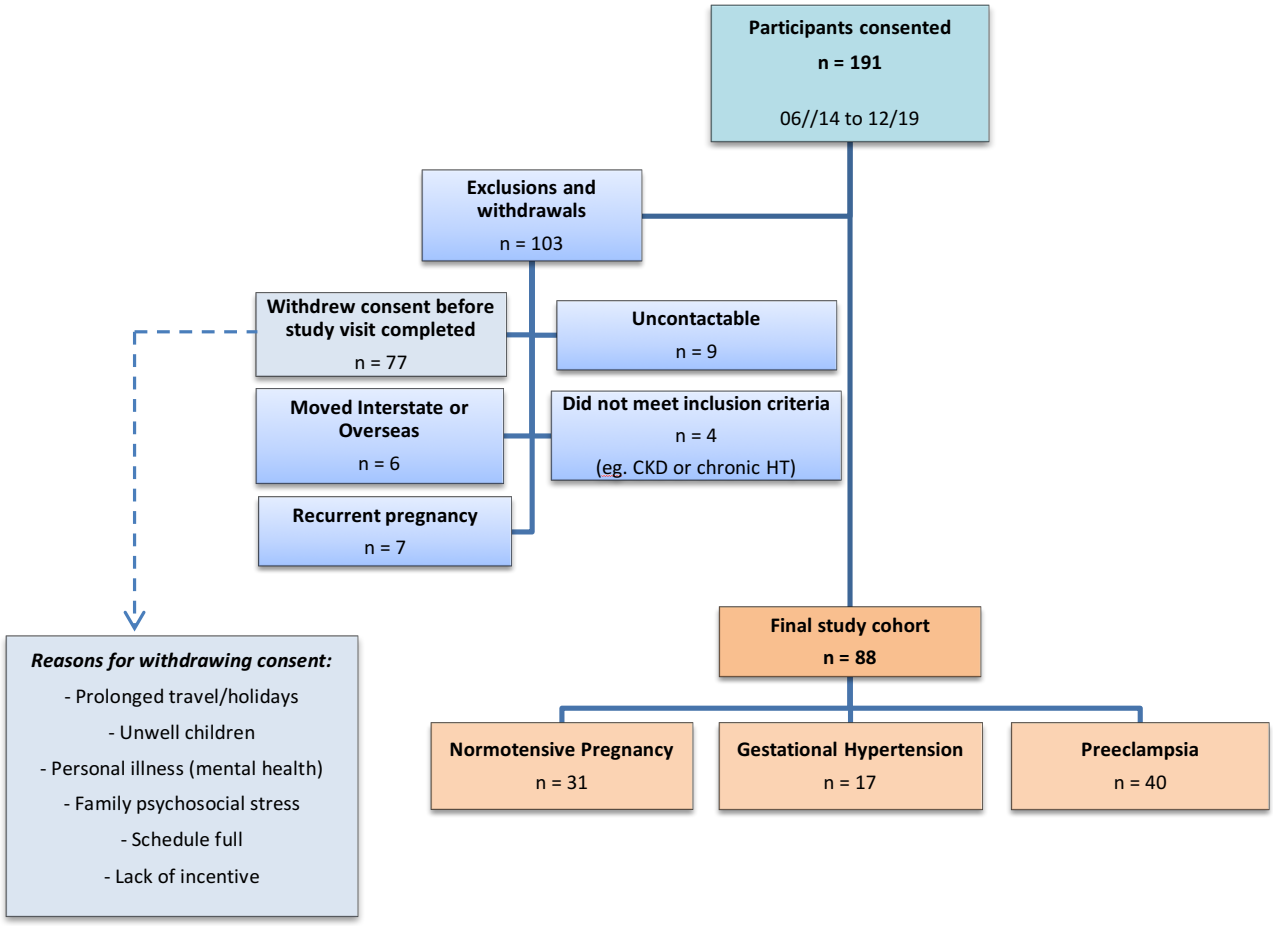


Table 3.1 Baseline maternal characteristics.

	Normotensive	Gestational HT	Preeclampsia	P
n	31	17	40	
Maternal characteristics				
Maternal age (years)	34 (30, 37)	34 (31, 37)	33 (28.5, 36)	ns
Ethnicity				
European	25 (80.1%)	17 (100%)	29 (72.5%)	ns
Asian	6 (19.4%)	0	4 (10.0%)	
South Asian	0	0	5 (12.5%)	
Oceanian	0	0	2 (5.0%)	
Education				
High school	6 (19.4%)	7 (41.2%)	11 (27.5%)	ns
Tertiary education	25 (80.1%)	10 (58.8%)	29 (72.5%)	
Socioeconomic index				
SEIFA score (by postcode)	1037 ± 36	1024 ± 43	1040 ± 38	ns
SEIFA score < Australian mean	7 (22.5%)	5 (29.4%)	5 (12.5%)	ns
SEIFA % rank within Victoria	76 (54, 83)	69 (48, 75)	75 (69, 82)	ns
Medical history				
Nuliparity	14 (43.8%)	6 (35.3%)	28 (71.8%)	0.024
Past history of HDP	1 (5.6%)	3 (27.3%)	5 (45.4%)	ns
Family history of hypertension	11 (34.3%)	4 (25.0%)	17 (42.5%)	ns
Assisted reproduction	3 (9.4%)	1 (5.6%)	0	ns
Current smoker	3 (9.4%)	1 (5.9%)	8 (20.5%)	ns
Body mass index (kg/m^2)	25 (22, 29)	33 (27, 36)	24.5 (22, 29)	0.002
Obesity (BMI > 30 kg/m^2)	7 (21.5%)	12 (70.5%)	8 (20.0%)	0.001
Type 1 diabetes	1 (3.1%)	1 (5.9%)	1 (2.6%)	ns
Hypothyroidism	0	2 (11.8%)	4 (10.3%)	ns
Breastfeeding	26 (81.3%)	11 (68.7%)	31 (77.9%)	ns
Breastfeeding duration (months)	4.0 (2.5, 6.0)	3.5 (0.8, 6.0)	3 (1.5, 6)	ns

Data expressed as frequency (%) for categorical variables and median (IQR) for continuous variables. Significance defined as $p < 0.05$ and determined by Chi-square and Kruskal-Wallis test. Definitions: hypertension (HT), body mass index (BMI), hypertensive disorder of pregnancy (HDP), socioeconomic indexes for areas score (SEIFA score).

Table 3.2 Maternal and perinatal birth outcomes

	Normotensive	Gestational HT	Preeclampsia	P
n	31	17	40	
Pregnancy outcomes: Mother				
Gestational diabetes	8 (25.8%)	6 (35.3%)	8 (20.5%)	ns
Induction	7 (30.4)	8 (57.1%)	24 (75.0%)	0.02
Birth mode				ns
Vaginal	17 (53.1)	6 (37.5%)	13 (32.8)	
Assisted vaginal	4 (12.5%)	1 (5.9%)	8 (20.5%)	
Elective Caesarean	7 (21.9%)	4 (23.5%)	2 (5.1%)	
Emergency Caesarean	4 (12.5%)	5 (29.4%)	17 (43.6%)	
Estimated blood loss (mL)	300 (150, 350)	500 (300, 800)	400 (300, 650)	0.005
Primary postpartum haemorrhage	1 (3.25%)	7 (41.2%)	10 (25.6%)	ns
Placental abruption	0	1 (5.9%)	0	ns
HDU admission mother	0	0	6 (15.4%)	ns
Postpartum readmission for HT	0	2 (11.8%)	7 (17.6%)	ns
Pregnancy outcomes: Baby				
Gestation (weeks)	39.3 (38.2, 40.3)	38.5 (38.2, 39.2)	38.4 (36.3, 39.4)	0.02
Preterm delivery	0	0	11 (28.2%)	0.01
% Male Baby	18 (60.0)	7 (43.8%)	21 (52.8%)	ns
Stillbirth	0	0	1 (2.6%)	ns
Birthweight (g)	3374 (3001, 3605)	3500 (3050, 3620)	2950 (2486, 3340)	0.003
Small for gestational age	3 (9.7%)	1 (5.9%)	9 (22.5%)	ns
Apgar 1min	9 (8, 9)	9 (7, 9)	9 (7, 9)	ns
Apgar 5min	9 (9, 9)	9 (8, 9)	9 (9, 9)	ns
SCN admission baby	2 (6.4%)	1 (5.9%)	10 (26.3%)	0.04

Data expressed as frequency (%) for categorical variables and median (IQR) for continuous variables. Significance defined as $p < 0.05$ and determined by Chi-square and Kruskal-Wallis test. Definitions: hypertension (HT), high dependency unit/critical care (HDU), special care nursery (SCN).

Table 3.3 Office blood pressure evaluation between hypertensive and normotensive pregnancies

	Normotensive pregnancy	Hypertensive pregnancy (GH or PE)	p
n	31	57	
Time postpartum (months)	7.8 (6.8, 10.8)	8.8 (6.1, 10.8)	ns
Antihypertensive therapy	0	10 (17.5%)	0.013
Office BP			
Number completed	31 (100%)	57 (100%)	
Systolic	121 ± 13	132 ± 14	0.001
Diastolic	73 ± 8	80 ± 9	0.006
MAP	89 ± 9	97 ± 11	0.001
Office BP Category			
Normotension (BP < 120/80)	14 (45.1%)	11 (19.3%)	0.013
Elevated BP (BP 120-129/80)	7 (22.6%)	7 (12.3%)	
Stage 1 hypertension (BP 130-139/80-89)	6 (19.4%)	22 (38.6%)	
Stage 2 hypertension (BP > 140/90)	4 (12.9%)	17 (29.8%)	

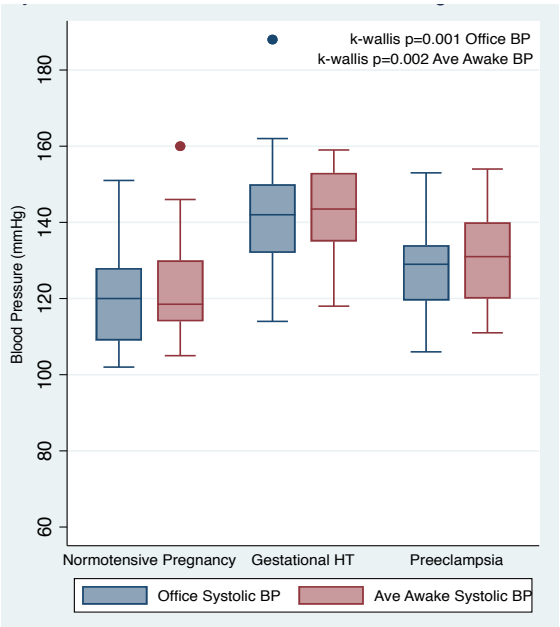
Data expressed as median (IQR), and frequency. Significance determined with t-test, Mann-Whitney or chi-square test, significance specified as $p < 0.05$. Definitions: mean arterial pressure (MAP), gestational hypertension (GH), preeclampsia (PE), blood pressure (BP)

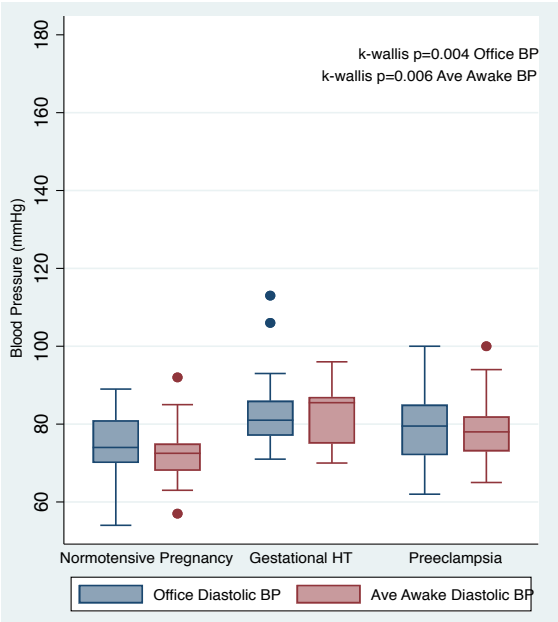
Table 3.4 Office blood pressure evaluation between gestational hypertension, preeclampsia and normotensive pregnancies.

	Normotensive pregnancy	Gestational HT	Preeclampsia	p
n	31	17	40	
Time postpartum (months)	7.8 (6.5, 10.9)	8.4 (5.4, 10.5)	8.4 (5.4, 10.7)	ns
Antihypertensive therapy	0	6 (35.3%)	4 (10.0%)	0.01
Office BP				
Number completed	31 (100%)	17 (100%)	40 (100%)	
Systolic	121 ± 13	143 ± 16	128 ± 11	0.001
Diastolic	73 ± 8	84 ± 11	78 ± 9	0.004
MAP	89 ± 9	104 ± 12	95 ± 9	0.002
Office BP Category				
Normotension (BP < 120/80)	14 (45.1%)	1 (5.9%)	10 (25.0%)	0.001
Elevated BP (BP 120-129/80)	7 (22.6%)	1 (5.9%)	6 (15.0%)	
Stage 1 hypertension (BP 130-139/80-89)	6 (19.4%)	5 (29.4%)	17 (42.4%)	
Stage 2 hypertension (BP > 140/90)	4 (12.9%)	10 (58.8%)	7 (17.6%)	

Data expressed as median (IQR), and frequency. Significance determined with t-test, Mann-Whitney or chi-square test, significance specified as $p < 0.05$. Definition: mean arterial pressure (MAP)

Figure 3.2 Postpartum office systolic and diastolic blood pressure





Box and whisker plot with median, IQR and range. Kruskal-wallis analysis of variance was used to compare pregnancy groups.

Table 3.5 Ambulatory blood pressure evaluation

	Normotensive pregnancy	Gestational HT	Preeclampsia	p
n	31	17	40	
Time postpartum (months)	7.8 (6.5, 10.9)	8.4 (4.1, 10.5)	8.4 (5.1, 10.7)	ns
24-hr Ambulatory BP monitoring				
Device tolerability				
Number attempted	24 (77.4%)	15 (88.2%)	35 (87.5%)	ns
Satisfactory test	21 (87.5%)	13 (86.7%)	30 (85.7%)	ns
Poor sleep quality	3 (12.5%)	3 (20.0%)	4 (11.4%)	ns
Would have ABPM test again for research	17 (70.8%)	5 (33.3%)	21 (60.0%)	ns
Would have ABPM test again for medical indication	19 (79.1%)	10 (58.8%)	30 (85.7%)	ns
24-hr average				
Systolic BP	118 ± 12	137 ± 12	127 ± 11	0.001
Diastolic BP	69 ± 6	79 ± 7	74 ± 6	0.005
MAP	85 ± 8	98 ± 9	91 ± 7	0.002
Heart rate	78 (72, 85)	77 (67, 79)	78 (71, 80)	ns
Daytime average				
Systolic BP	122 ± 13	141 ± 12	131 ± 12	0.002
Diastolic BP	72 ± 7	83 ± 7	77 ± 7	0.006
MAP	89 ± 9	102 ± 9	95 ± 8	0.002
Heart Rate	81 ± 8	77 ± 9	80 ± 9	ns
Stage 1 HT (BP > 130/80)	3 (13.6%)	0	2 (5.7%)	0.001
Stage 2 HT (BP > 135/85)	4 (18.1%)	11 (78.6%)	17 (48.6%)	0.001
Nighttime average				
Systolic BP	106 (100, 116)	127 (118, 132)	112 (106, 124)	0.007
Diastolic BP	60 (54, 70)	70 (63, 75)	65 (59, 69)	0.006
MAP	74 (67, 85)	89 (80, 94)	80 (76, 89)	0.009

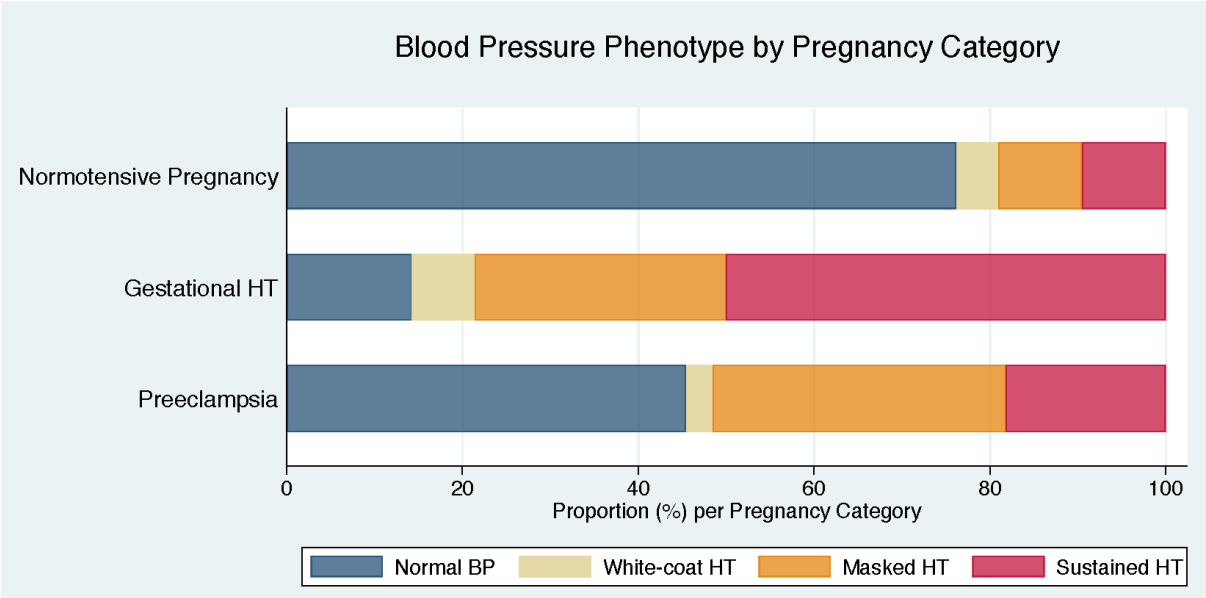
Data expressed as median (IQR), and frequency. Significance defines as $p < 0.05$ and determined by Kruskal-Wallis non-parametric analysis of variance. Definitions: hypertension (HT), 24-hour ambulatory blood pressure (ABPM), mean arterial pressure (MAP), blood pressure (BP).

Table 3.6 Blood pressure phenotype by pregnancy category

	Normotensive pregnancy	Gestational HT	Preeclampsia	p
n	22	14	35	
Antihypertensive therapy				
Currently taking antihypertensives	0	6 (42.8%)	4 (12.1%)	0.01
Blood pressure phenotype				
Normal blood pressure	17 (77.3%)	2 (14.3%)	17 (48.6%)	0.008
White coat hypertension	1 (4.6%)	1 (7.1%)	1 (2.8%)	
Masked hypertension	2 (9.1%)	4 (28.6%)	11 (31.4%)	
Sustained hypertension	2 (9.1%)	7 (50.0%)	6 (17.1%)	

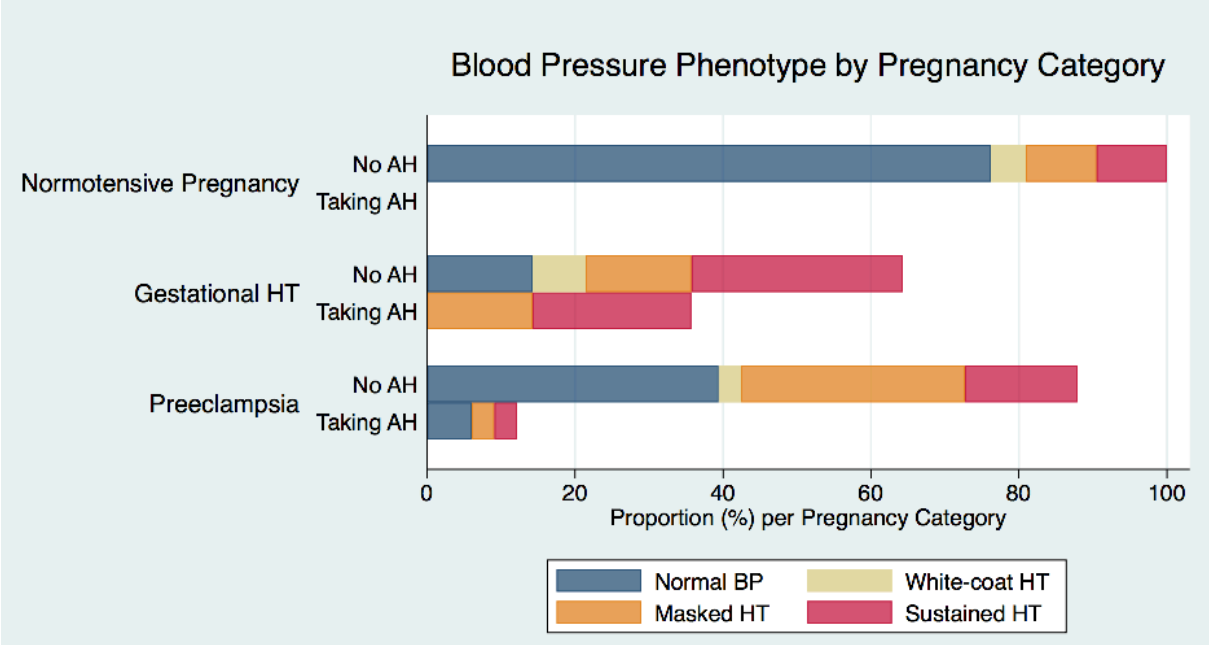
Data displayed as frequency (%) per pregnancy category. Chi-square with Kruskal-wallis test to compare groups.

Figure 3.3 Blood pressure phenotype by pregnancy category



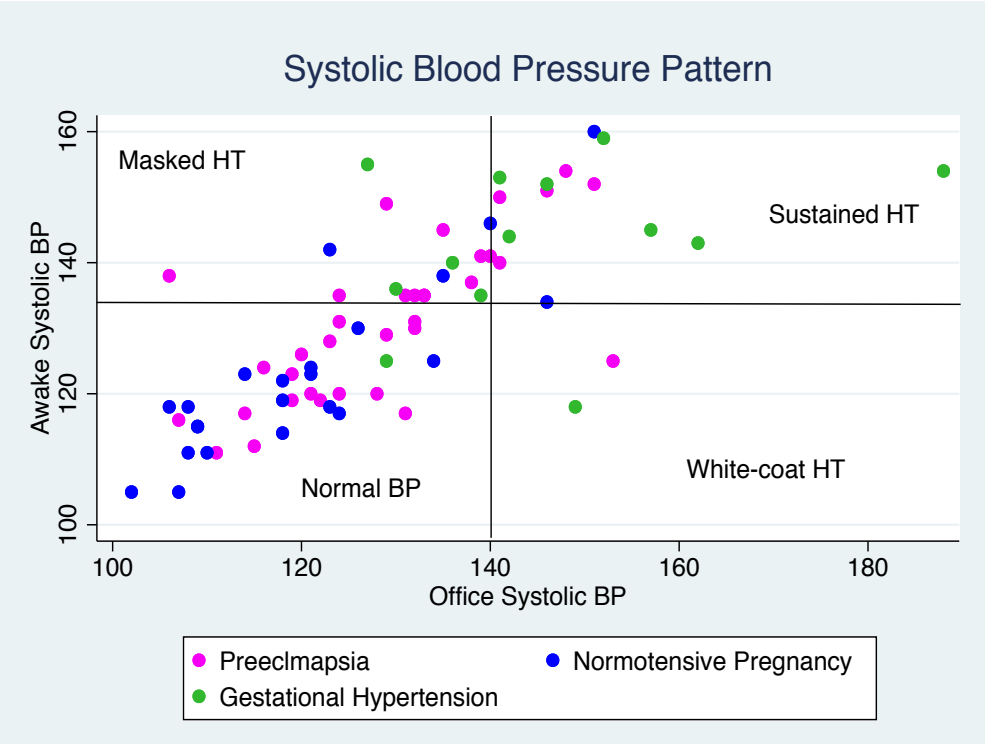
Data displayed as frequency (%) per pregnancy category.

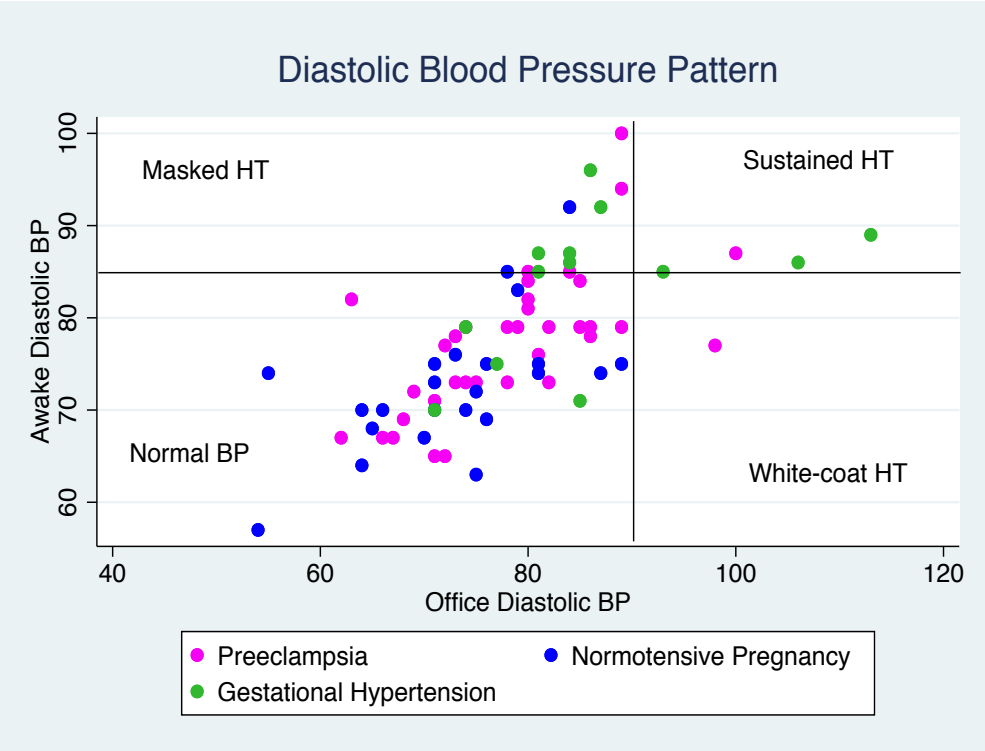
Figure 3.4 Blood pressure phenotype by pregnancy category and antihypertensive use



Data displayed as frequency (%) per pregnancy category. Definitions: antihypertensives (AH), hypertension (HT), blood pressure (BP)

Figure 3.5 Distribution of blood pressure phenotypes after hypertension in pregnancy





Blood pressure phenotype by pregnancy category. Systolic and diastolic blood pressure measured in mmHg.

Table 3.7 Odds ratio for masked hypertension in women with a history of hypertension in pregnancy with Stage 1 hypertension on office BP

	Odds Ratio for masked HT versus normal BP (average awake >135/85 versus <135/85 mmHg)	p
Office BP		
Stage 1 HT versus normal or elevated BP (130-139/80-89 versus <130/80 mmHg)	13.1 (95% CI 2.89-59.7)	0.001

Table 3.8 Circadian blood pressure patterns

	Normotensive pregnancy	Gestational HT	Preeclampsia	p
n	21	14	33	
Nocturnal blood pressure pattern				
Normal dipping	14 (66.7%)	9 (64.3%)	16 (48.5%)	ns
Non-dipping	4 (19.0%)	4 (28.6%)	12 (36.4%)	
Reverse dipping	1 (4.7%)	1 (7.4%)	2 (6.0%)	
Extreme dipping	2 (9.5%)	0	3 (9.1%)	

Data displayed as frequency (%) per pregnancy category. Chi-square with Kruskal-wallis test to compare groups.

Figure 3.6 Proportion of circadian blood pressure pattern by pregnancy group

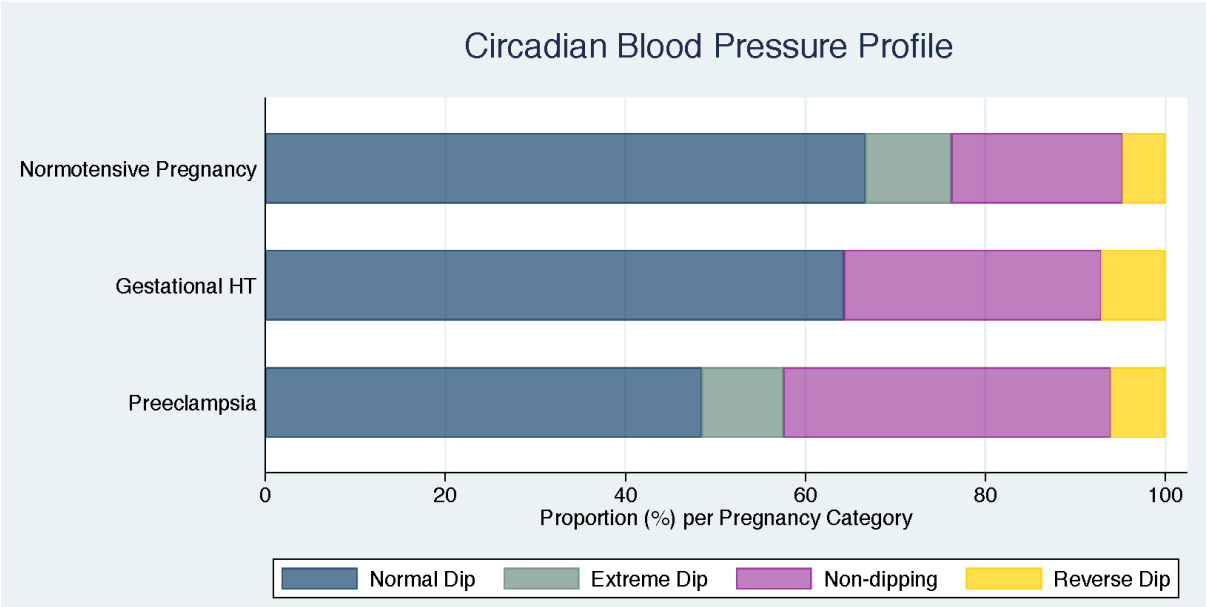


Table 3.9 Biomarkers of cardiovascular risk and endothelial dysfunction.

	Normotensive pregnancy	Gestational HT	Preeclampsia	p
n	31	17	40	
Time postpartum (months)	7.8 (6.5, 10.9)	9.4 (4.1, 10.5)	8.4 (5.1, 10.7)	ns
Creatinine	62 (59.5, 65.5)	68 (64, 75)	64 (55, 71)	ns
Calculated eGFR ($mL/min/m^2$)	111.2 (103.6, 115.6)	98.7 (88, 106.3)	111.4 (97, 118.3)	ns (0.053)
Uric acid	0.25 (0.23, 0.31)	0.36 (0.29, 0.38)	0.28 (0.23, 0.35)	0.003
ALT	16 (13, 22)	18 (13, 22)	19 (15, 23)	ns
uACR (mg/mmol)	0.7 (0.5, 1.3)	1.2 (0.5, 1.7)	1.2 (0.5, 3.4)	ns
uPCR (g/mmol)	0.01 (0.007, 0.01)	0.01 (0.007, 0.01)	0.01 (0.007, 0.011)	ns
sEndoglin (pg/mL)	5.4 (4.8, 6.7)	5.9 (3.8, 6.5)	4.7 (4.7, 6.5)	ns
sFlt-1 (pg/mL)	433 ± 70	458 ± 147	406 ± 96	ns
VCAM1 (ng/mL)	512 ± 140	495 ± 149	524 ± 178	ns
Myeloperoxidase (ng/mL)	21.8 ± 4.5	22.4 ± 5.9	23.4 ± 10.7	ns
Copeptin (ng/mL)	0.53 ± 0.15	0.47 ± 0.31	0.61 ± 0.45	ns

Data expressed as median (IQR) or mean ± SD. Significance defined as $p < 0.05$ and determined by Kruskal-Wallis or ANOVA. Definitions: estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), urine albumin:creatinine ratio (uACR), urine protein:creatinine ratio (uPCR).

Table 3.10 Comparison of clinical ISSHP diagnosis for hypertension in pregnancy and the discharge summary classification

	Normotensive	Gestational HT	Preeclampsia
Actual Classification: ISSHP 2018			
	31	17	40
Discharge Summary Classification: VPDC			
Normotensive pregnancy	29	4	4
Gestational HT	1	10	12
Preeclampsia	1	3	24
Misclassified			
	2	7	16

Discharge summary pregnancy diagnosis is directly reported to the Victorian Perinatal Data Collection (VPDC).

Table 3.11 Sensitivity and specificity of medical record diagnosis relative to actual clinical diagnosis.

	Percentage, 95 % CI
Preeclampsia Discharge Summary Classification (VPDC) accuracy	
Sensitivity	60.0 % (43.3 – 75.1)
Specificity	91.7 % (80.0 – 97.7)
Gestational Hypertension Discharge Summary Classification (VPDC) accuracy	
Sensitivity	62.5% (35.4 – 84.8)
Specificity	80.3 % (68.6 – 89.1)
Hypertensive Disorder of Pregnancy Discharge Summary Classification (VPDC) accuracy	
Sensitivity	85.9 % (73.8 – 93.6)
Specificity	90.9 % (75.0 – 98.0)

Hypertensive disorders of pregnancy refers to either a gestational hypertension or preeclampsia diagnosis.

Table 3.12 Prevalence of self-reported follow-up including blood pressure check after hypertensive pregnancy by time of NASCENT study visit.

	Gestational hypertension	Preeclampsia
No formal follow up	9 (52.9%)	13 (32.5%)
Follow-up with doctor	8 (47.1%)	27 (67.5%)
Specilist clinic	0 (0%)	16 (40.0%)
Family doctor	8 (47.1%)	11 (27.5%)

Chapter 4

MATERNAL COMMUNITY HEALTH CHECK STUDY

4.1 STUDY 1: Maternal postpartum follow-up survey

4.1.1 ABSTRACT

Background: Current Victorian models of postnatal care recommend a comprehensive 6-week infant and maternal health assessment by either a general practitioner or obstetrician. Aims of this study were to determine where, when and how postpartum maternal health checks were conducted in a population of local women.

Methods: A voluntary survey was conducted amongst mothers attending community vaccination sessions facilitated by local councils with their infants in Melbourne, Australia. Mothers were asked whether they had had a 6-week postpartum check, who it was with, and whether they had their blood pressure checked.

Results: 60 women were surveyed at a median of 8 months postpartum (range 1.75 - 12 months). 44 out of 60 (71.7%) women recall having a 6-week check with a doctor, specifically either an obstetrician or a general practitioner. Of the women who saw a doctor, 55.8% recalled having had their blood pressure checked. Of the 6 women who self-reported hypertension in their most recent pregnancy, 2/3 recall having seen a doctor for a 6-week check, however half did not have their blood pressure checked at this consultation.

Conclusion: Despite guideline recommendations, women do not always receive a 6-week postpartum maternal health check. Receiving this medical assessment does not guarantee review of blood pressure, even after experiencing pregnancy hypertension. This highlights some key pitfalls in the follow-up after complicated pregnancies, which may be targeted in future strategies to improve postpartum care.

4.1.2 INTRODUCTION

The World Health Organisation, in addition to national and international guidelines recommend women undergo a health check of both physical and psychological health at around 6-weeks postpartum (245). In Australia, the majority of postpartum health checks are completed by general practitioners (246). Many guidelines recommend a blood pressure check for all women, regardless of whether they experienced hypertension in pregnancy. The findings of Chapter 3 suggested that this postpartum check may not occur in all women, and also may not include a blood pressure check in a proportion of cases, which is important in the long-term care of women after hypertension in pregnancy. This study aimed to further understand the pathways of follow-up in the local population of postpartum women.

4.1.3 METHODS

After gaining approval from both local council and the human research and ethics committee, a voluntary survey was conducted amongst mothers attending community vaccination sessions in Melbourne, Australia. Immunisation sessions were facilitated by local council nursing staff in Whitehorse and Maroondah local government areas, and families attended with their infants for fully-funded routine vaccinations. After vaccination was completed, families were required to wait for 15 -20 minutes to ensure their infant has no adverse reaction prior to leaving. During this waiting-time, attending mothers were invited to participate in an anonymous short survey on their postpartum follow-up. Women who were from 4 to 12 months postpartum were asked whether they recall having had a 6-week postpartum check, who it was with, and whether they had their blood pressure checked. They were also asked if they recalled experiencing hypertension in pregnancy. Results were analysed using descriptive statistics.

4.1.4 RESULTS

A total of 60 women were surveyed at a median of 8 months postpartum (range 1.75 - 12 months). Of the women surveyed, 4 had delivered overseas but returned to Australia within 8 weeks of giving birth. 44 out of 60 (71.7%) women recall having a 6-week check with a doctor, specifically either an obstetrician or a general practitioner (Figure 4.1.1). Of the women who saw a doctor, 55.8% recalled having had their blood pressure checked. Of the 6 women who self-reported hypertension in their most recent pregnancy, 2/3 recall having seen a doctor for a 6-week check, however half did not have their blood pressure checked at this consultation.

4.1.5 DISCUSSION

This short survey was effective in characterising the general pathways for follow-up after birth in a local population of women. It also confirmed observations made in the NASCENT study (Chapter 3), which suggested that a number of women may not undergo a 6-week postpartum health check after complicated pregnancy. This observation is contrary to a report from 1996 in Australia suggesting 96% of women attend a 6-week postpartum check, although era differences in practice may account for this observed variation (247).

Other studies have also observed reduced attendance at the 6 –week postpartum check in both local and international settings (248, 249). Compared to women who attended their 6-week visit, risk factors for not attending an appointment are being younger, less educated, having a lower income, being a smoker, and having a home birth (173). Poor adherence to antenatal care appointments was also a risk factor.

The content of the 6-week postpartum check is highly variable, with different recommendations existing from different guidelines on content. As an example, blood pressure measurement is recommended for all women in some guidelines, but only for those who experienced pregnancy hypertension in others. Translating this into practice, an Australian study reported 68% of postpartum assessments to included measurement of blood pressure, which is similar to findings in this survey (250). In addition to variation

in guidelines, other factors which may affect consultation content from the literature include underestimation of the time required for postpartum consultation, and failure to receive communication from hospital relating to the birth episode and complications (235, 236, 251).

The necessity of the 6-week postpartum check has been questioned by some as there is limited evidence to support a benefit in long term maternal and child health (246). That being said, this general comment does not consider women and infants who require specific follow-up of either a chronic health condition or intrapartum or postpartum complications. Specific authorities such as SOMANZ and ADIPS are clear in their recommendations for postpartum follow-up after common pregnancy-related conditions such as diabetes and hypertension, to allow for screening and management of chronic disease and further education (71, 165).

Another observation was that many women in the survey delivered overseas, and had relocated soon after birth. This may be an important factor impacting longitudinal engagement with healthcare, and relocation to other states or countries was also observed to be a cause of study withdrawal in the NASCENT study for a number of women.

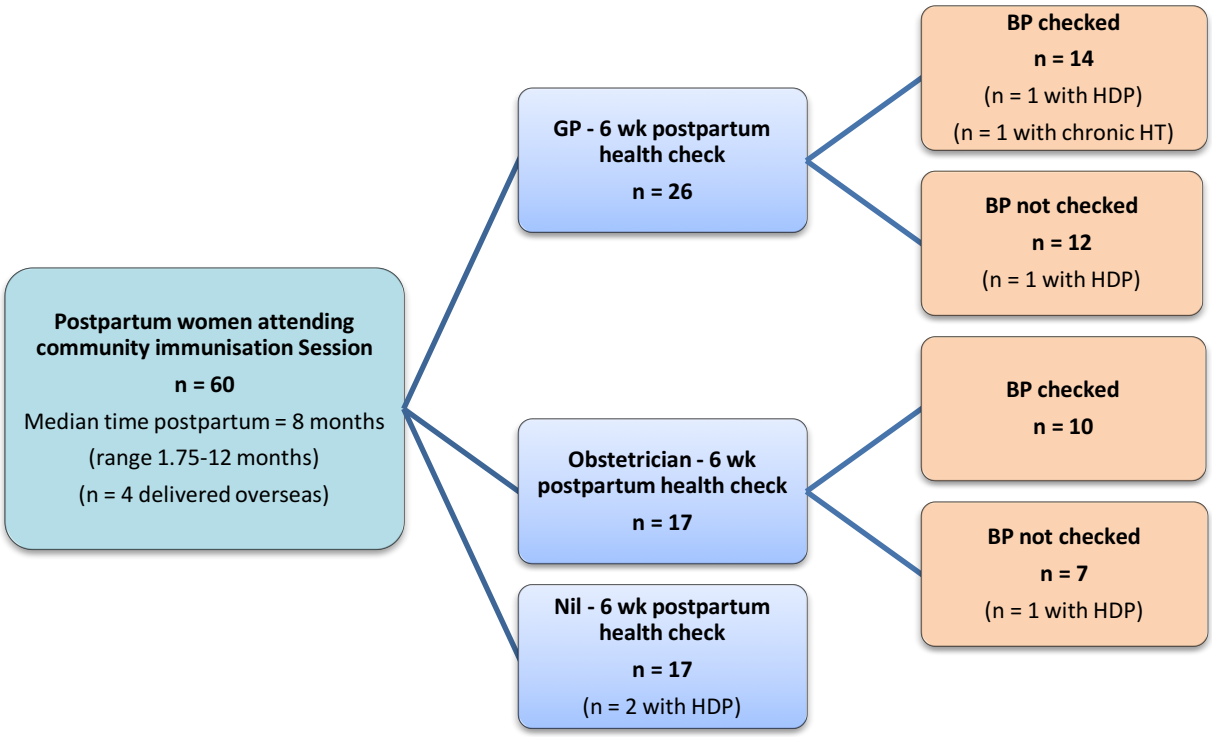
4.1.6 CONCLUSION

Despite guideline recommendations, women do not always receive a 6-week postpartum maternal health check. Receiving this medical assessment does not guarantee review of blood pressure, even after experiencing pregnancy hypertension. Factors potentially impacting the content of the health check include time and adequate communication between hospitals and general practitioners. These findings highlight some key pitfalls in the follow-up after complicated pregnancies, which may be targeted in future strategies to improve postpartum care.

4.1.7 ACKNOWLEDGEMENTS

The author would like to acknowledge the support of the Immunisation Teams at both Whitehorse and Maroondah City Councils for assistance with subject identification.

Figure 4.1.1 Postpartum follow-up survey results



4.2 STUDY 2: Maternal community cardiovascular health check study

4.2.1 ABSTRACT

Background: Timely postpartum follow-up of hypertensive disorders of pregnancy and gestational diabetes (GDM) is important for ensuring long term maternal health and a guideline recommendation. Aims of this study were to determine if inclusion of a short maternal health screen to routine maternal and child health (MCH) child visits was feasible in identifying women who may benefit from further follow-up after pregnancy, and to determine the population prevalence of uncontrolled hypertension.

Methods: A maternal health screen was integrated into routine 8-month MCH child visits. The health screen included obtaining demographic information, questions on hypertension and diabetes in pregnancy, and measurement of blood pressure and body mass index. Women with abnormal results (BP >140/90 mmHg or no GDM follow-up to date) were referred to their general practitioner (GP) for follow-up. Feasibility and acceptability were further evaluated through interview and qualitative survey of participating MCH nurses.

Results: 508 health screens out of 575 eligible 8-month visits (88.3%) were completed. 10.4% of completed assessments had abnormal results triggering GP-referral. Mean blood pressure was 114/72 ± 12.6/12.6 mmHg, and 6.9% of women had stage 2 hypertension. Risk factors for stage 2 hypertension were obesity (OR 5.8, 95%CI 2.7-12.6), a history of diabetes/GDM (OR 2.7, 95%CI 1.3-5.5), and hypertensive pregnancy (OR 9.7, 95%CI 4.6-20.4). Hypertensive pregnancy was reported by 12.0% (60 of 508 women), and over a third reported they had not undertaken a follow-up blood pressure check with a doctor since delivery. Surveyed nurses reported they were comfortable completing the assessments, mothers were highly receptive to participating, and felt the health check did not deviate from the core goals of MCH care or negatively impact workflow. Qualitative feedback key themes included: 'simple and easy to integrate', 'time may be a barrier to universal implementation', 'strong enthusiasm and appreciation from mothers'.

Conclusion: This study highlights the need for improved postpartum follow-up after complicated pregnancies, with 1 in 10 women screened being referred for further

management. It also demonstrates that targeted maternal health screening is feasible and acceptable in the MCH setting, and has capacity to reach a substantial proportion of the target population. Incorporating maternal health promotional activities such as screening and education into the MCHS setting both identifies women at risk of diabetes and future cardiovascular disease, and is a pragmatic and beneficial use of existing services.

4.2.2 INTRODUCTION

A quarter of all pregnancies in Australia are affected by hypertension and/or gestational diabetes. Timely follow-up of these conditions after delivery is essential in ensuring long-term maternal health and to reduce risks associated with unmanaged chronic disease during future pregnancies. Findings of the NASCENT study suggest that many women after hypertensive pregnancy are at risk of chronic hypertension, and may not receive timely follow-up of medical complications after delivery.

National and international guidelines on the management of hypertension in pregnancy and gestational diabetes recommend specific follow-up of these conditions within 3 months of birth. Women with gestational diabetes have a 2% risk of type 2 diabetes in the first year after birth and a 30% risk of gestational diabetes in subsequent pregnancies (74). In recognition of this, a 75g oral glucose tolerance test is advised by 12 weeks postpartum to exclude type 2 diabetes (71).

Hypertensive disorders of pregnancy include gestational hypertension and preeclampsia, and are not only associated with risk of recurrence in subsequent pregnancies, but also with both short and long-term maternal health risks which are potentially modifiable. These include chronic hypertension and metabolic syndrome in the years after birth, and premature maternal cardiovascular disease in the longer term. Timely postpartum follow-up allows screening for resolution of hypertension and other abnormalities such as proteinuria, to exclude coexisting diseases such as chronic kidney disease, and to provide counselling on risk of recurrence and planning for future pregnancy.

Prevalence of chronic hypertension after hypertensive pregnancy varies in the literature, but is often quoted to be 15-40% (3, 4). Guidelines recommend that persisting postpartum hypertension undergo screening for secondary causes in the absence of a known cause, as essential hypertension in young women is a diagnosis of exclusion (43, 83).

Patient, health service, community, and system factors may potentially influence the likelihood of an individual attending follow-up after a complicated pregnancy. These include factors such as: type and setting of advice given, health literacy and education level of the individual, absence of symptoms, availability of specialised follow-up clinics,

engagement with and access to primary healthcare services, and communication between maternity hospitals and primary healthcare providers.

When considering these potential factors and exploring angles to improve follow-up, it is valuable to examine factors motivating health behaviours in this population. Mothers in the postpartum period have been shown to strongly appreciate continuity-of-care, and prioritise their children's health over their own (237, 252). This is further supported by the observation that the majority of health encounters in the first six months after birth are for the infant's health rather than a mothers' own, and that maternal and child health nurses were seen more commonly than a general practitioner or obstetrician (238, 253).

Although maternal physical health is not traditionally the domain of maternal and child health services (MCH), there may be capacity to expand their role in promoting maternal health through facilitating and encouraging follow-up after complicated pregnancies. MCH services are uniquely positioned to engage with postpartum women as this services is both highly accessible and well-attended by the target population, and staffed by well-trained nurses specialising in midwifery in addition to child and family health.

Maternal and child health services are a primary healthcare service which is free for all Victorian families with children from birth to school-age to access. Core goals of MCH care provision are to promote the physical, emotional and mental health of mothers and families, and to provide education and support and oversee child development. Victoria has some of the highest participation and retention rates for this service in Australia, with 89% of families participating at 4 months postpartum, 85% at 8 months, and 79% at 12 months postpartum (254).

Aims of this study were to determine both the population prevalence of stage 2 hypertension and feasibility of including a short maternal health screen to routine 8-month MCH child visits to help identify women who may benefit from further follow-up after hypertension and diabetes in pregnancy.

4.2.3 METHODS

Nurses from 13 maternal and child health centers across two eastern Melbourne municipalities were recruited and trained to perform maternal health screens as part of routine child visits. Participation from nurses was voluntary and written consent was given. The health screen was performed during the 8-months child visit. This appointment was chosen for a number of reasons: it permitted time for the health check, few women would likely have recurrent pregnancy, participation rates are still high in MCH by 8 months, and the timing postpartum allowed for hypertension to resolve and women to have had sufficient time to seek their own follow-up.

For all eligible 8-month visits, MCH nurses were requested to complete a data collection sheet even if they did not complete a health assessment. This captured reasons for the health assessment not taking place, such as insufficient time or the mother not being present at the visit. Attending mothers were invited to undergo the health screen and verbal consent was obtained.

The maternal health screen comprised of: basic demographic information, determining a history of hypertension and diabetes and postpartum follow-up, measurement of blood pressure and body mass index. Women with abnormal results (BP >140/90 mmHg or no GDM follow-up to date) received a letter advising attendance with their general practitioner (GP) and listing sources of online education. Regular formal safety monitoring was carried out by the primary researcher ensuring appropriateness in handling of abnormal results. Results were evaluated with descriptive statistics and logistic regression.

Feasibility and acceptability were evaluated using a mixed methods design. At the conclusion of the study, participating MCH nurses undertook a short voluntary survey evaluating their perceptions and experiences. The survey contained a quantitative component with responses graded using a 5-point Likert scale, and qualitative component with open-ended questions. A semi-guided group discussion with MCH nurses and interview with MCH Team Leaders was also undertaken. Conversations were recorded and later transcribed. Key themes were identified from various qualitative data sources, and discussed based on the number of respondents identifying each issue.

Convergences across various key meta-themes from both qualitative and qualitative observations were identified, and agreement or dissonance between these themes were analysed using a triangulation protocol.

4.2.4 RESULTS

508 health screens out of 575 eligible 8-month visits (88.3%) were completed between October 2018 and March 2019, with an even distribution between recruitment sites (Figure 4.2.1). Most frequent reasons for assessments not being performed were time constraints and the mother not being present at the visit. The mean time taken per assessment was 5.0 ± 1.0 minutes.

Interpreters were used in a small number of assessments and the recurrent pregnancy rate was low at 2.4% (Table 4.2.1). Few women were current smokers (2.4%), and the majority of women breastfed for longer than 3 months (82.8%). A higher body mass index and a higher rate of obesity was seen in participants from Maroondah MCH.

Mean peripheral pressure was 114/72 ± 12.6/12.6 mmHg. There was a difference between sites relating to diastolic blood pressure, however systolic pressure was comparable (Table 4.2.2). Stage 2 hypertension was present in 35 (6.9%) of participants. Half of those with hypertension reported a history of hypertension in their most recent pregnancy. Of the women who were found to be hypertensive and reported a history of hypertensive pregnancy, a third reported they had not had follow-up with a doctor of their blood pressure postpartum. 60 (12.0%) of all participants reported a history of hypertension in their most recent pregnancy, of these, 37.5% reported they had not received follow-up with a doctor. Chronic diabetes was uncommon, however gestational diabetes was common with 18.7% prevalence. Of those who experienced gestational diabetes, 20.0% reported they had not had follow-up defined as having undertaken a postpartum oral glucose tolerance test.

Risk factors for stage 2 hypertension were examined (Table 4.2.3). Strong risk factors included obesity and a history of hypertension in pregnancy. Breastfeeding was negatively associated with hypertension. Given obesity is a strong risk factor and

potential cause of hypertension, a second model adjusting for body mass index showed hypertensive pregnancy to remain a strong risk factor, independent from obesity.

A 7-question voluntary survey was completed by participating nurses at the conclusion of the study. 60% (n=27) of nurses who participated completed surveys, and were the same group of nurses to participate in qualitative group discussion. Non-respondents were either on leave, had recently retired or changed jobs. Responding nurses generally overestimated the number of assessments they had completed (Figure 4.2.2). Nurses also reported that mothers were highly receptive to participating, nurses were comfortable performing the health check, and felt it did not deviate from the core goals of MCHS care or negatively impact workflow (Figure 4.2.3).

Key themes were identified based on the number of respondents highlighting these themes as issues (Table 4.2.4). The number of times a theme was mentioned and specific quotes outlining the contextual basis are listed. A number of these key themes converged with themes and issues identified from the health screen data and quantitative survey data. Whilst there were many aspects of agreement across various data sources within these themes, there were also aspects of dissonance (Table 4.2.5). 'Time' was the meta-theme most frequently mentioned and also displaying aspects of dissonance across data sources. Health screens were demonstrated to take a short amount of time to complete, and nurses indicated they felt that health screens had minimal negative impact on consultation length or work-flow. That being said, in qualitative feedback a number of nurses expressed that time was still a barrier to being able to offer the health screen to more women, particularly to those with complex psychosocial backgrounds. Other aspects such as sharing equipment or equipment failure were also mentioned as time-related factors.

4.2.5 DISCUSSION

Findings of this study highlight both the prevalence of hypertension among postpartum women, and the need for improved postpartum follow-up after pregnancies complicated by diabetes or hypertension. 1 in 10 women screened were referred to

their general practitioner for further follow-up of either uncontrolled hypertension or gestational diabetes. Incorporating the health screen into the maternal child health setting was also feasible, whereby 88.9% of the eligible women attending were able to be screened with minimal impact on consultation length, nurses were both comfortable and competent in completing health screens safely, and nurses and clients were happy to perform and undertake the health screens. Additional findings were that women with hypertension were more likely to report a history of pregnancy hypertension, have a higher body mass index, and were less likely to breastfeed.

Uncontrolled hypertension prevalence in this population using a traditional threshold of a blood pressure >140/90 mmHg was 6.9%. Blood pressure was measured using a community-screening type-protocol which required a 1-2 readings to make this diagnosis and trigger referral. Whilst this pragmatic approach to blood pressure measurement may slightly over-estimate the true prevalence of hypertension, similar results are reported in other community screening programs involving Australian women of childbearing age. Results of a national screening program revealed rates of uncontrolled hypertension to be 6.7% in women aged 18-24, 8.2% in 25-34 year-olds, and 13.9% in 35-44 year olds (45).

Additional findings of this study confirmed those seen in Chapter 3: NASCENT study of suboptimal follow-up after hypertensive disorders of pregnancy. In this study, follow-up after gestational diabetes was also evaluated and shown to have room for improvement.

Follow-up of gestational diabetes in particular has recently benefitted from the introduction of a more formalised pathway to follow-up, clear evidence-based national guidelines, and a strong push to improve communication between maternity units, individuals and general practitioners (71). For example in the catchment areas in which this study was undertaken, standard follow-up procedure consists of women receiving a letter and a pathology request at their last antenatal diabetes clinic appointment. The letter provides instruction on how and when to organise their postpartum follow-up glucose tolerance test. Results are sent to their general practitioner and the antenatal diabetes clinic, who contact women if there is an abnormal result, and they do not need to see their doctor if results are normal. Despite the relatively straightforward follow-up

pathway, 20.0% of the women participating in this study stated they had not had their oral glucose tolerance test by 8 months postpartum. This indicates that despite clear follow-up pathways existing in this catchment area, there is still room for improvement.

A discord between antenatal and peripartum care and communication, with postpartum care has been suggested as a factor deleterious to ensuring postpartum follow-up after medical complications in pregnancy. In addition to this, there is ongoing shortening of average length-of-stay after vaginal delivery in Australia from 5.3 days in 1991, to 3.5 days in 1999, and as of 2010 this had further reduced to 2 days (255-257). In recognition of this and to emphasise the importance of integration and continuity-of-care, it has been suggested by some the postpartum period be re-labelled the "4th trimester". The postpartum period is a time of rapid change in lifestyle and responsibilities, and research on the health behaviours of this population suggest a strong appreciation for continuity-of-care, and maternal tendency for prioritisation of their children' health over their own (237, 258). With this in mind, Maternal and Child Health services is well-positioned to promote maternal health by encouraging follow-up after complicated deliveries, as they develop a lasting and continuous relationship with women from soon after birth. There may also be potential to include basic targeted health screening as occurred in this study.

Although the main focus of Maternal and Child Health care is traditionally on child health and development, a strong secondary focus is on health of the entire family. An important point to make is that the most common medical complications of pregnancy (gestational diabetes, hypertension and obesity), can potentially impact the health of multiple family members in the short and long term, and can largely be considered potentially modifiable. Offspring of pregnancies affected by diabetes and hypertension have been shown to have higher rates of metabolic syndrome and higher blood pressure than their peers in childhood and adolescence (259). Although no clear evidence currently exists on how to best modify risk for either offspring or mothers after hypertension or diabetes in pregnancy, it is likely that lifestyle modification and instilling lasting good health behaviours will remain cornerstones in management, and are unlikely to cause harm.

Obesity, another important health issue in pregnancy often co-exists and has a potential causative role with both gestational diabetes and hypertension in pregnancy. There is evidence for lifestyle modification in the management of obesity in postpartum women to reduce risk of adverse pregnancy outcomes in subsequent pregnancies (208, 209, 260). It is well-recognised that obesity is commonly a household issue, and so a logical setting to optimise child and family health through healthy lifestyle education or on-referral could be the Maternal and Child Health services. This concept is further supported by feelings and thoughts expressed by MCH nurses in this study, whereby increasing a focus on maternal health brought opportunity to integrate discussion of relevance for the whole family such as healthy eating and lifestyle behaviours.

The concept of incorporating maternal health screening and promotional activities into existing child health assessment models may also be a useful tool in the developing world. Maternal health follow-up after complicated pregnancies has been shown to be particularly poor despite many countries utilising formalised follow-up arrangements such as postpartum clinics.

An additional potential unmeasured benefit of this study worth mentioning was to increase awareness of these important maternal health issues amongst otherwise healthy mothers, MCH nurses, and general practitioners. This may also have a beneficial follow-on effect in increasing general community awareness.

Feasibility of the maternal health screen was demonstrated in this study. The health screen fit within established care pathways, nurses completed the health checks competently, quickly, safely, enjoyed performing them, and a large proportion of the target population were able to be captured by screening. However, effectiveness and benefit of maternal health screening were not captured in this study. Longitudinal data on the effectiveness of referrals and recommendations by evaluating whether advice was acted on would be useful in evaluating effectiveness. Whether maternal health screening has an impact on long term maternal health or birth outcomes in future pregnancies would be a much harder research question to answer. Postpartum women are often reluctant to participate in experimental research, and randomisation to a non-

intervention arm may be unethical as growing evidence amounts demonstrating long term health risks after complicated pregnancies (241).

Limitations of this study include reliability of data. Participant recall bias was possible as may data points required self-reporting by clients. Some data collection sheets from nurses were incomplete. Other factors such health literacy and education may also be factors in accurate participant self-reporting. As an example, 12 of 508 clients reported they were 'unsure' if they had had hypertension (or "high blood pressure") in pregnancy, indicating these participants may have had limited understanding of some health terms and be a potential factor leading to poor follow-up.

Other limitations include the restricted number of data items captured, and depth of information acquired for each item. Items such as ethnicity, parity, antihypertensive use, activity level, education level, family structure and supports, if collected may have given a more complete picture of maternal postpartum health. As examples, Whitehorse City Council provides services to a high proportion of Asian families in comparison to Maroondah. In contrast, Maroondah City Council services a catchment with families from more diverse socioeconomic backgrounds as defined by residential SEIFA score. Although increasing the number of data items captured may have given a more complete understanding of the population, it was felt the time and complexity added to the health screen in acquiring these extra items would detract from the simplicity and core aims of demonstrating feasibility and proof-of-concept.

A number of potential barriers to wider implementation of the health screen were identified in survey feedback and group discussion. These mostly centred around perceived time and resource shortages, as this health screen would add to existing tasks and funding allocations. This potential barrier, and others such as how to best approach clients with sensitive issues such as obesity, were generally felt to be surmountable by MCH nurses. Nurses also expressed a desire to have more tools and resources to educate and act on abnormal findings. Potential future directions proposed are to develop maternal health-focussed modules for the MCH Smartphone App, and to lobby for improvement and update of the existing consumer information available on the

Victorian Government sponsored Better Health Channel website and the Raising Children website.

4.2.6 CONCLUSION

Follow-up after complicated pregnancies has room for improvement. Nurse-initiated maternal health screening in the primary healthcare setting to improve follow-up after complicated pregnancies is both a feasible and pragmatic use of existing services, and may help identify women at risk of diabetes and future cardiovascular disease. While this type of community-based health screen does not replace formalised follow-up after medical complications in pregnancy, it will likely be complimentary and have added benefits in increasing community awareness of these important health issues.

4.2.7 ACKNOWLEDGEMENTS

I would like to acknowledge the contributions of Maternal and Child Health Team Leaders at Whitehorse and Maroondah City Councils, Ms Pam Heselev and Ms Vicki Middleton in supporting and facilitating this research project. Additional acknowledgement is given to the 45 MCH nurses who participated in this study by undertaking the health screens. This research project was financially supported by the Eastern Health Foundation Elaine and Frank Derwent Memorial Research Grant in 2017. This work was presented at the Society of Obstetric Medicine of Australia and New Zealand Annual Scientific Meeting in October 2019, where I received the Presidents' Prize for best clinical research presentation by a junior SOMANZ member.

Figure 4.2.1 Flow chart for maternal health check study

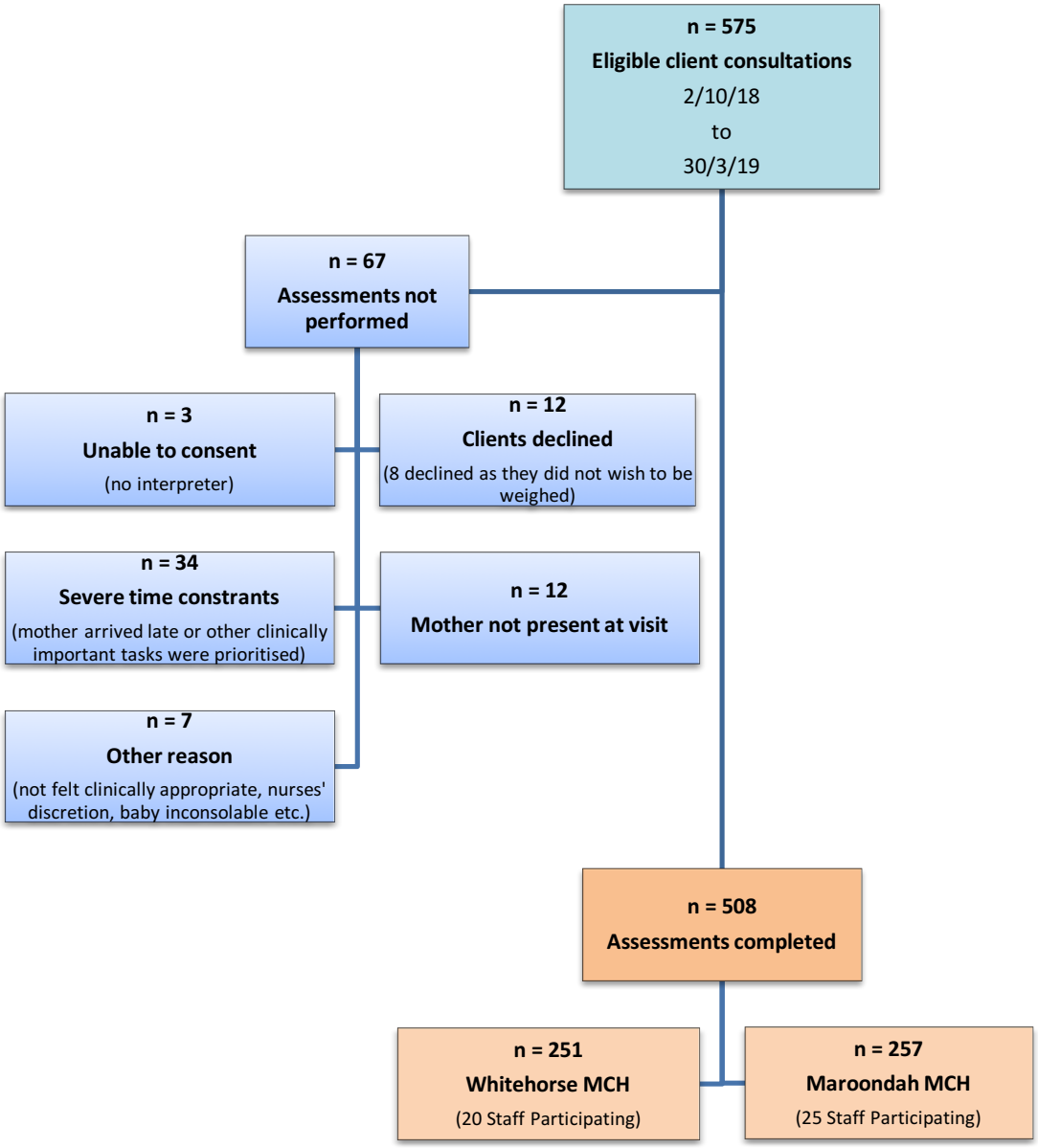


Table 4.2.1 Maternal health checks - baseline characteristics and demographics

	Whitehorse MCH	Maroondah MCH	p	Overall
Eligible appointments	279	296		575
Assessments completed	251	257		508
Interpreter	7 (2.5 %)	2 (0.7 %)	ns	9 (1.8 %)
Time taken for Ax (mins)	5.0 ± 1.0	5.0 ± 1.0	ns	5.0 ± 1.0
Abnormal screen for Rx	18 (7.3%)	35 (13.7%)	ns	53 (10.6%)
Demographics				
Maternal age (years)	34 ± 4.3	33 ± 4.2	ns	33 ± 4.3
Currently pregnant	6 (2.4%)	6 (2.4%)	ns	12 (2.4 %)
Smoking				
Current	3 (1.2%)	9 (3.6%)	ns	12 (2.4%)
Previous smoker	38 (15.2%)	51 (20.24%)	ns	89 (17.7%)
Breastfeeding				
Nil breastfeeding	18 (7.2%)	22 (8.8%)	ns	40 (8.0%)
Less than 3 months	19 (7.6%)	27 (10.8%)		46 (9.2%)
More than 3 months	214 (85.6%)	200 (80.0%)		414 (82.8%)
Body mass index	23.1 (20.8, 26.5)	24.6 (21.9, 28.7)	0.01	23.9 (21.4, 27.7)
Obesity (BMI >30 kg/m^2)	31 (12.5%)	43 (17.6%)	ns	74 (15.0%)

Definitions: assessment (Ax), referral (Rx), body mass index (BMI), maternal and child health (MCH). Chi-square, t-test and Mann-Whitney-U used as appropriate.

Table 4.2.2 Maternal health checks - blood pressure and diabetes

	Whitehorse MCH	Maroondah MCH	p	Overall
Eligible appointments	279	296		575
Assessments completed	251	257		508
Blood Pressure				
Peripheral systolic BP (mmHg)	114 ± 12.5	113 ± 12.7	ns	114 ± 12.6
Peripheral diastolic BP (mmHg)	69 ± 10.5	75 ± 10.9	0.001	72 ± 12.6
Stage 2 HT (BP > 140/90 mmHg)	10 (4.1 %)	25 (9.7 %)	0.011	35 (6.9 %)
HT and HDP	4/10 (40.0%)	14/25 (56.0%)		18/35 (51.4%)
HT, HDP and no follow-up	1/4 (25.0%)	4/13 (30.7%)		5/17 (29.4%)
Hypertensive pregnancy	25 (10.0%)	35 (14.0%)	ns	60 (12.0%)
No follow-up HDP	9/21 (42.8%)	12/35 (34.3%)		21/56 (37.5%)
Diabetes				
Chronic diabetes	2 (0.8%)	2 (0.8%)		4 (0.8 %)
Gestational diabetes	51 (20.2%)	44 (17.2%)		95 (18.7%)
No follow-up GDM	8/48 (16.7 %)	10/42 (23.8%)		18/90 (20.0%)

Definitions: assessment (Ax), referral (Rx), body mass index (BMI), gestational diabetes (GDM), hypertensive disorder of pregnancy (HDP), hypertension (HT), blood pressure (BP), maternal child health (MCH). Chi-square, t-test and Mann-Whitney-U used as appropriate.

Table 4.2.3 Risk factors for stage 2 hypertension.

	Unadjusted Odds Ratio	Adjusted Odds Ratio
Maternal age	1.02 (0.94-1.11)	1.05 (0.96-1.15)
Body mass index	1.16 (1.09-1.23)	-
Obestity (BMI > 30 kg/m^2)	5.86 (2.72-12.62)	-
Diabetes (GDM or chronic)	2.68 (1.29-5.54)	1.88 (0.82-4.32)
Current smoking	1.29 (0.16-10.32)	0.88 (0.18-7.57)
Breastfeeding	0.35 (0.14-0.92)	0.47 (0.16-1.40)
Hypertension in pregnancy	9.66 (4.57-20.44)	6.45 (2.78-14.93)
Augmentation index	1.01 (0.96-1.04)	1.02 (0.98-1.06)

Unadjusted odds ration with 95% confidence interval. Second model adjusts for body mass index.

Figure 4.2.2 MCH nurses' survey question on estimated number of health checks

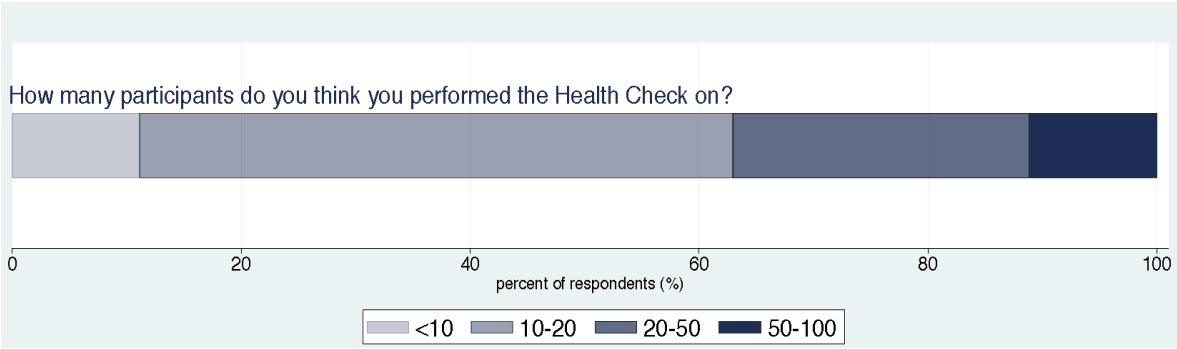
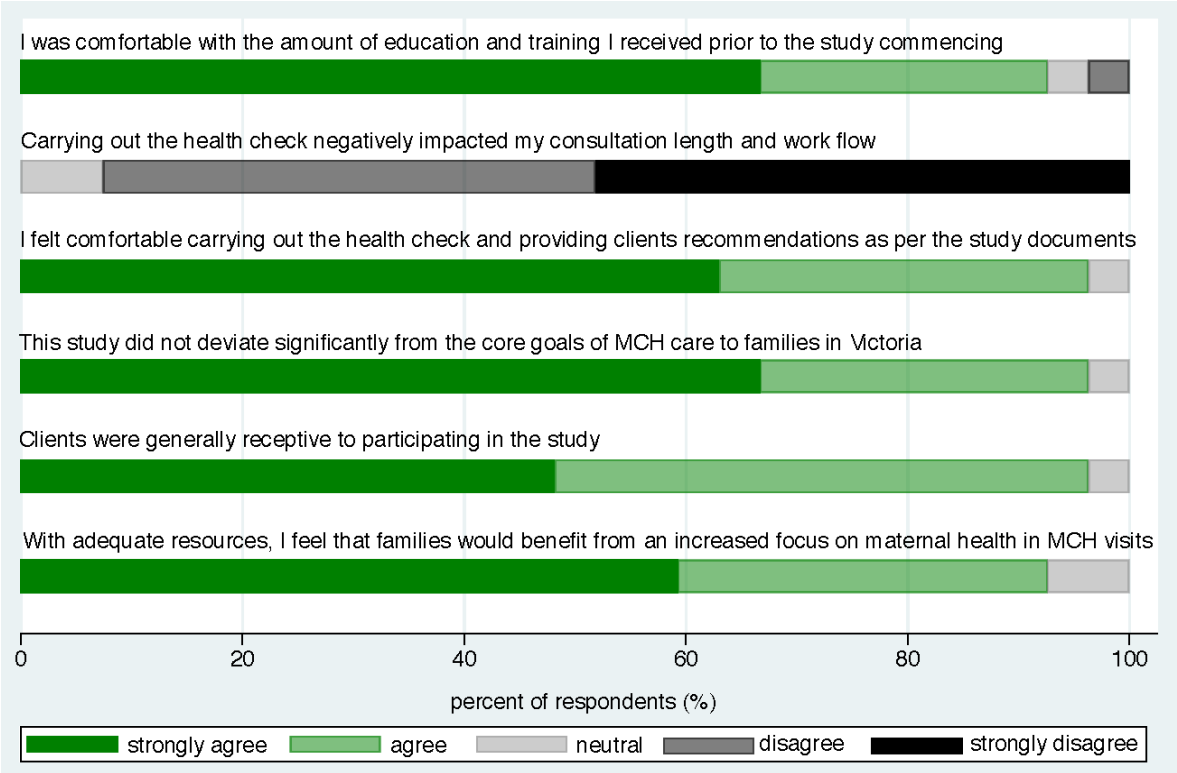


Figure 4.2.3 MCH nurses' survey on experiences and perceptions of participating in the study



Respondents answered survey questions with a 5-point Likert scale as displayed. (n = 30, 66.6% of participating MCH nurses completed survey)

Table 4.2.4 Key themes with sample quotes identified from qualitative survey and groups discussion.

Key themes	Number of respondents mentioning each factor		Sample quotes
	Survey	*Interview*	
Issues encountered			
Equipment issues	2	5	*"Sometimes the BP cuff was too small with the obese clients."* *"BP machine sometimes would not record, so I had to check the BP twice."*
Obesity	3	6	*"Women who were overweight would not want to participate."* *"Weight for clients who were obese was an issue. Weighing gave opportunity to discuss weight and refer these clients somewhere for help with this."* *"Most of the families I had that refused to be part of the study did so because they did not want to be weighed."*
Conflicting advice	1	3	*"Women had been given different advice from their OBG – ie. hypertension in pregnancy won't have an effect later in life and won't be an issue for subsequent pregnancies."*
Barriers to implementation			
Time	19	8	*"Time (is a barrier), especially when clients arrive late for appointments and have complex issues."* *"A few times the mothers had too many issues to be able to do the study, but it was rare."* *"Time factor. Each room should have their own BP machine. I could have done more however I couldn't find the BP machine – it wasted time."* *"Doing the health check increased time during some consultations. Suggest varying the visit so there are more options: 3-month, 8-month, 12-month etc."* *"If busy, I forgot to complete the data sheet fully. Sorry."* *"The study didn't really add any time to my consults and was easy to explain and conduct."*
Families want to focus on children	2	1	*"Mothers often want to focus on their babies."* *"Often parents' focus is on their children which makes it hard to talk about maternal health."*
Funding	4	5	*"Lack of support from higher management often stops projects like this progressing."*

Key themes	Number of respondents mentioning each factor		Sample quotes
	Survey	***Interview***	
Other comments			
Integration	4	7	*"I just added a bit more to what I would normally do in asking re: diabetes and BP (I usually already ask about BP follow-up but do not measure)."* *"I feel if it was part of our normal practice and we spoke about women's health checks, participation would increase."* *"Such a GREAT project and very important information to empower women to be proactive in their own wellbeing. I would be happy to integrate this information/process into normal sessions if time allows."* *"The study was simple and easy to integrate into my normal consultations. I feel it was also effective in showing that postpartum care needs improvement."*
Opportunity	5	10	*"It was a good time to encourage mothers to focus on themselves rather than the baby."* *"(the study) gave me opportunity to build on the other Women's Health items we already do."* *"Great experience and opportunity to further talk (to mothers) about their health and the impact on their health."* *"I also had two clients with symptomatic low BP, the study gave me opportunity to talk about their own health and send them to see their GP."*
Appreciation	9	13	*"The mothers enjoyed participating in the study and were happy to be seen as a priority for baby's wellbeing."* *"All the mothers I invited to do the study were very enthusiastic."* *"The study was well-received by the mothers and the feedback was very positive. I did not have any clients who did not want to participate."* *"The mothers on the whole appreciated discussing the issues and having the follow up."* *"I saw a mother last week at the 12-month visit. She'd had HT in pregnancy and had been on antihypertensives which were stopped at her 6-week check. She did the study at 8-months and HT was found. She saw her GP who verified HT and she went back on antihypertensives. She was very happy and grateful she was offered the health check and had opportunity to have her health improved."*

Table 4.2.5 Triangulation of meta-themes identified from quantitative and qualitative data

Meta-theme	Agreement or Dissonance	Comments
Time	Dissonance	○ Health screens were quick and completed within 5 minutes on average in a 45-minute consultation, which included explanation of the study, consent, and documentation ○ Quantitative survey and interview suggested consultation length was not affected by the study ○ Qualitative survey suggested time was a barrier to completing more health screens. This was often specifically for families with more complex issues, and would be mothers who may benefit the most from health screening
Focus on baby's health	Dissonance	○ Comments from qualitative survey suggest some families would prefer to keep focus on the baby's health ○ Other comments from interviews and qualitative survey suggest both mothers and nurses appreciated the opportunity to talk about maternal health, and felt it was important for heath of the family as a whole
Integration	Agreement	○ Survey data suggests nurses feel the study integrated with the core goals of MCH care ○ Interview comments suggested health screen compliments existing maternal health promotional aspects of MCH care, and was easy to integrate into routine consultations
Appreciation	Agreement	○ Quantitative survey data and interview data suggest that mothers were generally receptive, appreciative and enthusiastic about the health screen
Opportunity	Agreement	○ Survey and interview data suggests nurses saw the health screen as an opportunity to expand and consolidate their existing care and health education given to mothers ○ Some nurses also appreciated the opportunity to participate in research to progress knowledge in this area as they strongly advocate improving maternal health care
Obesity	Dissonance	○ Obesity was common, and higher BMI was a risk factor for hypertension ○ Nurse feedback suggests that a number of women did not want to participate in the health screen as it required weight measurement, or did not complete that part of the study as they were uncomfortable with being weighed ○ Interview discussions highlighted the opportunity and potential benefit that weight measurement gave to talk about healthy lifestyle for the whole family
Proof of concept	Agreement	○ Health screens demonstrated that hypertension was prevalent, and follow-up was suboptimal and could be improved ○ MCH nurses were comfortable and competent in completing the health screens ○ High participation rate (88.3%) meant that the majority of eligible women were screened ○ Qualitative feedback suggests some clients followed recommendations and had further management of their health condition (although effectiveness was not formally evaluated)

Chapter 5

PREGNANCY OUTCOMES IN CHRONIC HYPERTESNION

5.1 ABSTRACT

Background: Chronic maternal hypertension is associated with adverse maternal and perinatal pregnancy outcomes, and much of this morbidity is thought to be attributable to superimposed preeclampsia. This study aimed to determine the risk of pregnancy morbidity in a local population of women with chronic hypertension after adjustment for recognised independent risk factors for adverse pregnancy outcomes, and estimate the proportion of morbidity attributable to superimposed preeclampsia.

Methods: Women with chronic hypertension were identified from a database of 43,910 deliveries (2008-2018) from two maternity centers in Melbourne, Australia. In a matched cohort design, cases were matched for era, plurality and parity to controls. Associations between chronic hypertension and pregnancy outcomes were evaluated after adjustment for recognised risk factors including: site, age, body mass index (BMI), smoking, diabetes, renal disease, ethnicity, gestation at first antenatal visit, and previous preeclampsia. Additionally, the population attributable fraction of key adverse pregnancy outcomes to superimposed preeclampsia was determined.

Results: Pregnancy outcomes significantly associated with chronic maternal hypertension included: preeclampsia (OR 10.3, 95%CI 4.7-22.6), maternal ICU admission (OR 15.0, 95%CI 2.6-87.5), and intervention-related adverse events such as: induction of labour (OR 4.3, 95%CI 2.7-6.8), Caesarean section without labour (OR 2.3, 95%CI 1.5-3.3), and iatrogenic preterm delivery (OR 7.6, 95%CI 3.7-15.3). Important neonatal associations were: preterm delivery (OR 3.8, 95%CI 2.0-6.9), small gestational age (OR 2.9, 95%CI 1.7-4.9), and neonatal admission to SCU/NICU (OR 2.0, 95%CI 1.2-3.2). There was a significant negative association with normal vaginal delivery (OR 0.4, 95%CI 0.3-0.6). Outcomes with a higher fraction attributable to superimposed preeclampsia were maternal ICU admission and preterm delivery, however small for gestational age and neonatal SCN/NICU admission were minimally attributable.

Conclusion: Multiple adverse pregnancy outcomes were associated with chronic maternal hypertension after adjustment for recognised risk factors. Adverse neonatal outcomes in particular appeared to be independent of superimposed preeclampsia. This suggests pregnancy morbidity in chronic hypertension cannot be solely attributed to

preeclampsia. These findings confirm the need for pre-pregnancy counselling, early pregnancy risk stratification and fetal surveillance in these women.

5.2 INTRODUCTION

Chronic maternal hypertension is associated with adverse maternal and perinatal outcomes, and affects around 0.6% of pregnancies in Australia although this is likely to be an underestimation (46, 48, 175). Historically, the majority of this pregnancy morbidity was thought to be attributable to superimposed preeclampsia (176, 177).

Internationally, the incidence of chronic maternal hypertension in pregnancy seems to be increasing, and for example in the United States, rates have doubled over the last decade to an estimated prevalence of 2% (47, 179). Proposed contributing factors to this include the increasing average age of mothers and the increasing average body mass index of women giving birth. Little is known about the affect this may be having on trends in chronic maternal hypertension and pregnancy outcomes in Victorian women. A single epidemiological study exists examining an Australian population. This study was limited to deliveries in New South Wales between 2000 and 2002, and acknowledges a limitation of the dataset used being reduced sensitivity in identifying chronic maternal hypertension (46).

Chronic hypertension often coexists with other important maternal risk factors for adverse pregnancy outcomes. These risk factors may be independent of chronic hypertension such as smoking or ethnicity, or be factors that may potentially have a contributory role in the development of chronic hypertension, such as obesity or chronic kidney disease.

Considering these coexisting risk factors is important when evaluating pregnancy outcomes in women with chronic hypertension, and omitting adjustment for these co-factors is a common limitation of existing literature. This importance is further highlighted when considering how prevalent obesity, metabolic syndrome and smoking are amongst the modern era antenatal population (179, 209, 243).

Findings from both Chapters 3 and Chapter 4 suggest that the prevalence of chronic hypertension amongst postpartum women in the local population is higher than quoted

in the literature (46). This includes both the subgroups of women who either experienced a hypertensive disorder of pregnancy, or those who had normotensive pregnancy. Many of the women in both studies were either contemplating pregnancy or had recurrent pregnancy at the time of study enrollment. Providing accurate counselling and risk estimates for adverse pregnancy outcome is somewhat difficult in the absence of evidence relevant to the local population.

This study aimed to determine the risk of pregnancy morbidity in a local population of women with chronic hypertension after adjustment for recognised independent risk factors for adverse pregnancy outcomes, and estimate the proportion of morbidity attributable to superimposed preeclampsia.

5.3 METHODS

Using a database from two maternity centres in Melbourne, Australia, records on all deliveries over a 10-year period (2008-2018) were reviewed for a history of chronic maternal hypertension.

Cases of chronic maternal hypertension were identified from more than one source due to poor sensitivity of the primary database. This is a known limitation of the database specific to the identification of this parameter. The specific protocol for case identification and medical record review, including the use of a second reviewer to enhance validity is further discussed in Chapter 2.

After identification of chronic maternal hypertension, cases were matched in a ratio of 1:4 with women unaffected by chronic hypertension. Cases were matched for era (month of delivery), pleurality, and parity. Deliveries with major fetal anomalies or congenital defects were excluded.

Maternal baseline characteristics and pregnancy outcome data was collected from the chronic hypertension cases and matched cohort. Both maternal characteristics and outcome data was required to be documented in the primary dataset, and there was no additional medical record review. A list of these variables of interest is seen in Table 5.1.

Associations between chronic hypertension and pregnancy outcomes were evaluated by multivariable logistic regression analysis which included adjustment for baseline maternal characteristics. Adjustment variables for the multivariable model were selected if shown to have an association with chronic maternal hypertension using univariable logistic regression.

The regression model examining neonatal outcomes additionally adjusted for gestational diabetes given the known association with adverse neonatal outcomes and increased prevalence in the chronic maternal hypertension cohort.

Additionally, the population attributable fraction of various key adverse pregnancy outcomes to superimposed preeclampsia was derived from the prevalence and adjusted odds ratios.

5.4 RESULTS

230 singleton pregnancies affected by chronic maternal hypertension were identified in 186 women in the database of 43,910 deliveries. Prevalence of chronic hypertension was 0.52%.

Maternal pregnancy outcomes significantly associated with chronic maternal hypertension after adjustment for maternal baseline characteristics included preeclampsia (OR 10.3, 95%CI 4.7-22.6), induction of labour (OR 4.3, 95%CI 2.7-6.8), Caesarean section without labour (OR 2.3, 95%CI 1.5-3.3), and maternal high dependency (ICU) admission (OR 15.0, 95%CI 2.6-87.4) (Table 5.2). There was a significant negative association with normal vaginal delivery (OR 0.4, 95%CI 0.3-0.6). There was no association with postpartum haemorrhage or emergency Caesarean section.

A number of neonatal outcomes were significantly associated with chronic maternal hypertension after adjustment for baseline maternal characteristics and gestational diabetes (Table 5.3). These include: preterm delivery (OR 3.8, 95%CI 2.0-6.9), iatrogenic preterm delivery (OR 7.6, 95%CI 3.7-15.3), small gestational age (OR 2.9, 95% CI 1.7-4.9),

and neonatal high dependency (SCU/NICU) admission (OR 2.0, 95%CI 1.2-3.2). There was no significant association with stillbirth.

For each pregnancy outcome demonstrated to have a strong association with chronic maternal hypertension, the proportion of cases attributable to superimposed preeclampsia was determined. Outcomes with a higher fraction attributable to superimposed preeclampsia were maternal ICU admission and preterm delivery, however small for gestational age and neonatal SCN/NICU admission were minimally attributable (Table 5.4).

5.5 DISCUSSION

This study confirms the findings of other studies in demonstrating an association between adverse pregnancy outcomes and chronic maternal hypertension. Additional original contributions are to provide an estimate of the magnitude of pregnancy risk in a local population, to demonstrate that key adverse outcomes are independent of important potential confounders such as maternal age, obesity, renal disease, or gestational diabetes, and that certain crucial neonatal outcomes are minimally attributable to superimposed preeclampsia.

Preeclampsia incidence was significantly higher amongst women with chronic maternal hypertension compared to the matched cohort at 13.04% versus 1.13%. However, this rate was not as high as published in other populations. A recent meta-analysis demonstrated the pooled incidence to be 25.9%, however significant variation was noted amongst studies with quoted incidences ranging from 5.45% to 77.9% (178). Authors hypothesised this may be due to heterogeneity of study populations, or that determination of pregnancy outcomes and chronic hypertension may differ significantly between studies. An era effect may also be relevant as almost half the included studies were published last century, and a downward shift in gestational age at delivery in the modern era may potentially account for lower rates of preeclampsia at term (179, 261, 262).

Interestingly, although the incidence for preeclampsia was generally lower than other published cohorts, the odds ratio for preeclampsia was very similar. This suggests a

similar proportionate increase in risk from the background rate amongst women without chronic hypertension between studies with differing incidence rates (47).

In this study, the definition of chronic maternal hypertension used was relatively broad and included both women with longstanding histories of hypertension on multiple pharmacotherapies, and those with recent diagnoses sometimes made in the early stages of pregnancy. Additionally, there were high rates of intervention to induce delivery with a lower gestation in the chronic hypertension group compared to the matched cohort. Both delivery at a lower gestation and the determination of chronic hypertension used in this study may be factors contributing to the observed lower incidence of preeclampsia.

The incidence of preeclampsia was determined from the electronic hospital birth records in this study. Reduced sensitivity of this database for the diagnosis of pregnancy hypertension may also explain the lower incidence of preeclampsia in comparison to other published literature. This is a database of clinician-entered data which is reported periodically to the Victorian Perinatal Data Collection to maintain a statewide database of birth outcomes overseen by Consultative Council on Obstetric and Paediatric Mortality and Morbidity. Sensitivity and accuracy of this database and other Australian state birth databases has been shown to be reduced in the domains of pregnancy hypertension. In particular, sensitivity for the diagnosis of preeclampsia was shown to be between 61-84% (48, 175). A similar sensitivity for the diagnosis of preeclampsia using this database was also observed in the cohort from in Chapter 3.

A number of pregnancy outcomes were strongly associated with chronic maternal hypertension in statistical analysis. Aside from preeclampsia, there was a strong association with intervention-related outcomes in women with chronic hypertension, such as induction of labour and Caesarean section without labour. This is not unsurprising as uncontrolled hypertension is an indication for delivery, especially after 37 weeks' gestation, and can occur with or without superimposed preeclampsia in chronic maternal hypertension. This is also reflected in the strong association with iatrogenic preterm delivery.

The adjustment for confounders such as maternal age, chronic renal disease, obesity, and diabetes was important in evaluating pregnancy risks specific to chronic

hypertension, and a relative strength of this study. Each of these factors can coexist with chronic hypertension, and are also independently associated with increased pregnancy morbidity. The contribution of underlying chronic kidney disease as a potential competing risk factor to pregnancy morbidity in chronic maternal hypertension has been demonstrated by Bateman et al. and Sibai et al. Within these studies, women with chronic hypertension and a history of chronic kidney disease identified either through coding or by early-pregnancy proteinuria, had the highest rates of preeclampsia and adverse neonatal outcomes (47, 177). Sibai et al. also noted adverse neonatal outcomes were independent of superimposed preeclampsia.

Additionally, obesity has been demonstrated to also be an important cofactor often coexisting with chronic hypertension. In a local population of women obesity was shown to be highly prevalent, and 23.8% of all preeclampsia cases were found to be potentially attributable to obesity (263).

An aim of this study was to examine the interaction between preeclampsia and pregnancy morbidity in this cohort. A number of statistical methods exist to demonstrate this including: adjustment for superimposed preeclampsia in a regression model, using stratified analysis, or by determining the population attributable risk and fraction. In this study, determining the population attributable fraction was able to clearly demonstrate that outcomes such as maternal critical care admission were strongly related to by superimposed preeclampsia, whereas specific neonatal outcomes were largely independent of preeclampsia. The maternal association was not unsurprising given that pregnancy hypertension is the commonest indication for maternal critical care admission in Australia. Obstetric haemorrhage is the second most common indication, which is also often associated with pregnancy hypertension (264, 265).

The important neonatal outcomes of being small for gestational age and requiring admission to SCN/ICU were shown to be largely independent of superimposed preeclampsia. Other researchers have also reported an association between chronic maternal hypertension and intrauterine growth restriction or small for gestational age neonates, independent of superimposed preeclampsia (176, 266-268). This is not a universal finding in the literature however, with others showing no association (269,

270). A possible rationale for lower birthweight may be related to the long term vascular adaptions of chronic hypertension. In the presence of significant vascular remodeling in chronic hypertension, there may be reduced capacity to achieve the required physiologic vasodilation to facilitate normal placentation. This hypothesis would be supported by the observation that both elevated maternal blood pressure in first trimester (potentially a failure of physiologic vascular adaption), and a longer duration of chronic hypertension (higher risk for significant vascular remodeling) have been associated with lower birthweight, although this is not necessarily independent of superimposed preeclampsia (267, 271). Additionally, women with chronic hypertension who do not require pharmacotherapy in early pregnancy, presumably as evidence of normal physiologic adaption to pregnancy, have been shown to have no increased risk of small for gestational age neonates (268, 272).

Although adjustment for confounders was a potential strength of the study, not all potential confounders with biological plausibility were included in the final regression model. This was a tradeoff between minimising risk of Type 1 error due to model-overfitting, and adjusting for potential confounders which have biological plausibility however did not demonstrate statistical association with chronic hypertension in this cohort. An example variable is maternal smoking; although it plausibly can adversely influence pregnancy outcomes, it was a low-prevalence risk factor with no statistical association with chronic hypertension in this cohort, and so was not included in the adjusted regression model. A larger sample size would allowed for the use of further adjustment variables and more detailed stratified analysis, and is an aim for future work in this area.

Additional study limitations were that aspirin use and blood pressure control in early pregnancy which can potentially modify risk of adverse pregnancy outcome, were not captured across the entire cohort. Further to this, there was also a lack of stratification by essential or secondary chronic hypertension. Secondary hypertension has been associated with higher risk of pregnancy morbidity, however is also a relatively rare event (47). Due to this rarity and relatively small sample size, a stratified analysis of pregnancy outcomes by hypertension type was not feasible.

Although increased pregnancy morbidity is clearly demonstrated amongst women with chronic hypertension, a question unanswered by this study is how to best modify risk in this population. Risk prediction tools used in early pregnancy are often focused on identifying and reducing preeclampsia risk, however this analysis has demonstrated that pregnancy risk in chronic hypertension is not solely attributable to preeclampsia. Use of low dose aspirin has strong evidence for reducing preeclampsia risk in high-risk women. A number of smaller studies have also suggested that weight loss in those who are overweight and exercise may reduce preeclampsia risk, however it is unknown if this is beneficial in chronic hypertension (208, 260). Lower blood pressure without pharmacotherapy in early pregnancy in chronically hypertensive women is associated with less pregnancy morbidity, but it remains unknown if lower blood pressure induced by pharmacotherapy will reduce pregnancy risks in women presenting with uncontrolled blood pressure in first trimester to the same degree.

Considering all of these factors, women with chronic hypertension should have the opportunity of both pre-conception health optimisation and counselling, especially if considering fertility treatment. Best practice would include investigation for secondary causes of hypertension if not completed. Once pregnancy occurs, early pregnancy risk-stratification, aspirin use, and planning for increased maternal and fetal surveillance throughout pregnancy seem prudent.

5.6 CONCLUSION

Chronic maternal hypertension is associated with high rates of preeclampsia and intervention such as labour induction, Caesarean section and iatrogenic preterm delivery. Whilst much of the measured maternal morbidity can be explained by superimposed preeclampsia, adverse neonatal outcomes appear to be only partially attributable. These findings confirm the need for pre-pregnancy counselling, early pregnancy risk stratification and fetal surveillance in women with chronic maternal hypertension.

5.7 ACKNOWLEDGEMENTS

I would like to acknowledge the contributions of Dr Niamh Aherne as the second data reviewer, and Mr Adrian Yong Yao Tan (medical student) for assistance with coding to generate the matched cohort. This work was presented as an oral communication at the Society of Obstetric Medicine of Australia and New Zealand Annual Scientific Meeting 2018.

Table 5.1 Maternal and neonatal variables of interest

Baseline Maternal Characteristics	Pregnancy Outcomes	
Site	*Maternal*	Preeclampsia
Age		Gestational diabetes
Body mass index		Postpartum haemorrhage
Previous preeclampsia		Blood transfusion
Country of birth		Induction of labour
Chronic kidney disease		Mode of delivery
Pre-existing diabetes		Maternal ICU admission
Smoking	*Neonatal*	Preterm delivery/iatrogenic or spontaneous
Gestation at booking visit		Birthweight/Small gestational age
		Baby sex
		Neonatal SCN/NICU admission
		Stillbirth

Table 5.2 Maternal outcomes associated with chronic hypertension

	Normotensive controls	Chronic hypertension	Adjusted OR
n	920	230	
Maternal outcomes			
Gestational diabetes	100 (12.19%)	48 (26.3%)	ns
Preeclampsia	13 (1.14%)	30 (13.04%)	10.3 (4.7-22.6)
Preeclampsia with severe features	3 (0.33%)	14 (6.1%)	23.5 (5.7-96.7)
Maternal critical care admission	2 (0.22%)	9 (3.91%)	15.0 (2.6-87.4)
Induction of labour	218 (23.7%)	106 (46.09%)	4.3 (2.7-6.8)
Delivery			
Normal vaginal delivery	541 (58.8%)	81 (35.22%)	0.42 (0.3-0.6)
Assisted vaginal delivery	105 (11.4%)	27 (11.74%)	ns
Caesarean section without labour	162 (17.61%)	92 (40%)	2.3 (1.6-3.3)
Caesarean section in labour	110 (11.96%)	30 (13.04%)	ns
Emergency Caesarean section	118 (12.82%)	54 (23.47%)	ns
Postpartum haemorrhage			
Estimated blood loss (mL)	417 ± 230	493.23 ± 280	ns
Postpartum haemorrhage	159 (17.34%)	49 (21.49%)	ns
Severe postpartum haemorrhage	58 (6.32%)	25 (10.96%)	ns
Blood transfusion	17 (1.85%)	8 (3.48%)	ns

Frequency (%), mean ± SD, and adjusted odds ratio (OR). Adjusted for baseline maternal characteristics: maternal age, site, BMI, diabetes, renal disease, and previous preeclampsia

Table 5.3 Neonatal outcomes associated with chronic hypertension

	Normotensive controls	Chronic hypertension	Adjusted OR
n	920	230	
Neonatal outcome			
Gestation at delivery	39.4 ± 1.5	38.3 ± 2.2	ns
Placental abruption	2 (0.2%)	3 (1.3%)	ns
Preterm delivery	45 (4.9%)	29 (12.6%)	3.8 (2.0-6.9)
Iatrogenic preterm delivery	26 (2.8%)	26 (11.3%)	7.6 (3.7-15.4)
Spontaneous preterm delivery	19 (2.1%)	2 (0.9%)	ns
Birthweight (g)	3442 ± 517	3220 ± 676	ns
Small for gestational age	76 (8.3%)	33 (14.3%)	2.9 (1.7-4.9)
Baby sex (male)	468 (52.8%)	114 (49.6%)	ns
Neonatal critical/special care admission	98 (10.7%)	49 (21.4%)	2.0 (1.2-3.2)
Stillbirth	3 (0.3%)	1 (0.4%)	ns

Frequency (%), mean ± SD, and adjusted odds ratio (OR). Adjusted for baseline maternal characteristics: maternal age, site, BMI, diabetes, renal disease, previous preeclampsia, and gestational diabetes

Table 5.4 Population attributable fraction of significant maternal and neonatal outcomes due to superimposed preeclampsia

	Chronic hypertension without superimposed preeclampsia	Chronic hypertension with superimposed preeclampsia	Adjusted OR	Population attributable fraction
n	200	30		
Maternal outcomes				
Emergency Caesarean section	54 (27.0%)	13 (43.3%)	3.3 (1.4-7.3)	19.1%
Maternal ICU admission	3 (1.5%)	6 (20.0%)	19.7 (3.6-108.1)	67.0%
Neonatal outcomes				
Preterm delivery	11 (5.5%)	18 (60.0%)	22.8 (8.6-60.1)	56.4%
Small for gestational age	19 (9.5%)	11 (36.7%)	5.1 (2.0-12.9)	23.3%
Neonatal SCN/ICU admission	33 (16.5%)	16 (53.3%)	5.9 (2.5-14.0)	22.9%

Frequency (%), Odds ratio (OR) adjusted for recognised risk factors for adverse pregnancy outcomes: age, site, BMI, gestational diabetes, and renal disease. Definitions: intensive care unit (ICU), special care nursey (SCN)

Chapter 6

CLINICAL RISK FACTORS FOR SUPERIMPOSED PREECAMPSIA IN WOMEN WITH CHRONIC HYPERTENSION

6.1 ABSTRACT

Background: Chronic maternal hypertension is associated with a 3- to 5-fold increased risk of preeclamspia. The compounding effect of additional risk factors on incidence of superimposed preeclampsia in such patients is uncertain. It was hypothesised there may be significant clinical risk factors identifiable in early pregnancy which are associated with an increased risk of superimposed preeclampsia.

Methods: Clinical risk factors for preeclampsia identified at the pregnancy booking visit in women with known chronic hypertension were obtained from two obstetric centers in Melbourne, Australia. Risk factors included age, parity, previous preeclampsia, country of birth, smoking, secondary hypertension, renal disease/proteinuria, hypertension duration, diabetes, antihypertensive use at conception and/or first trimester, aspirin use before 16 weeks, blood pressure (BP) at booking, and body mass index (BMI). Associations were evaluated by univariate and multivariate logistic regression analysis.

Results: 233 births occurred in 186 women with chronic hypertension (0.55% prevalence). Preeclampsia occurred in 36 (15.5%) of these births, of which 19 (8.2%) had severe features. On univariable analysis, previous preeclampsia (OR 5.5, 95%CI 1.9-12.7) and hypertension chronicity > 5 years (OR 2.4, 95%CI 1.8-4.9) were most strongly associated with preeclampsia. Adjusting for site, age, parity, BMI, and renal disease, hypertension chronicity > 5 years remained an independent risk factor (OR 1.2, 95%CI 1.1-1.5), as did a previous history of preeclmapsia (OR 7.1 95%CI 2.1-24.6).

Conclusion: Preeclampsia risk in pregnant women with chronic hypertension is high, and historical features such as previous preeclampsia or a longer duration of hypertension may pose additional risk. This highlights the importance of pre-pregnancy counselling and careful clinical appraisal in early pregnancy in women with chronic hypertension to best direct appropriate gestational management.

6.2 INTRODUCTION

Chronic maternal hypertension is associated with a 3- to 5-fold increased risk of preeclampsia, although findings from the study in Chapter 5 suggest risk may be higher in a local population (47, 176-178). The compounding effect of additional risk factors on incidence of superimposed preeclampsia in such patients is uncertain.

Much of the maternal pregnancy morbidity in chronic hypertension was shown to be attributable to superimposed preeclampsia in Chapter 5. Whilst risk of superimposed preeclampsia was shown to be significantly elevated in a local population with chronic hypertension, it is also important to acknowledge that a substantial proportion of women also have uncomplicated deliveries at term. With this in mind, the ability to risk-stratify from early pregnancy may help prioritise and best-direct resources to benefit those at highest risk.

Previously identified risk factors for superimposed preeclampsia from observational studies include an elevated blood pressure at pregnancy booking visit (systolic BP > 130 mmHg OR 1.7, 95%CI 1.1-2.6), poorly-controlled blood pressure in first trimester, a past history of preeclampsia (OR 1.9, 95%CI 1.3-3.0 and OR 4.1, 95%CI 1.6-10.2), active smoking (OR 1.8, 95%CI 1.01-3.2), assisted reproduction, black ethnicity (OR 2.3, 95%CI 1.5-3.6), being overweight (BMI of 25-30 OR 1.7, 95%CI 1.1-2.8), and chronic kidney disease (177, 273-275).

Limitations of existing studies are that important causes of secondary hypertension such as chronic kidney disease which may confound results are inconsistently considered in the interpretation of findings.

Aims of this study were to determine if early-pregnancy clinical risk factors may be associated with an increased risk of superimposed preeclampsia in women with a history of chronic hypertension in a local population. Specific factors of interest are clinical risk factors easily-identifiable at the pregnancy booking visit, and may be considered non-modifiable or potentially modifiable.

6.3 METHODS

Birth episodes for women with chronic hypertension were identified within a pregnancy database of 43,910 deliveries at two maternity centres in Melbourne, Australia over a 10-year period (2008-2018).

Cases of chronic maternal hypertension were identified from more than one source due to poor sensitivity of the primary database. This is a known limitation of the database specific to the identification of this parameter. The specific protocol for case identification and medical record review, including the use of a second reviewer to enhance validity is further discussed in Chapter 2.

Maternal baseline characteristics and risk factors for preeclampsia were identified from detailed medical record review. Definitions used are described in Chapter 2. Specific risk factors of interest included both non-modifiable and potentially modifiable factors, including a number of novel risk factors such as duration of hypertension and antihypertensive use at conception. These risk factors are listed in Table 6.1.

Associations between risk factors and superimposed preeclampsia were evaluated by univariable and multivariate logistic regression analysis. Adjustment covariates were selected either as they were demonstrated to have a significant association with preeclampsia in univariable analysis, or due to biological plausibility. Chronic kidney disease was once such variable which did not demonstrate significance in univariable analysis in this study. However, as it is well-established to be independently associated with preeclampsia in other cohorts, it was included in the multivariable model for this study.

Certain continuous exposure variables underwent further evaluation by dichotomisation at specific thresholds of known clinical significance. Examples included maternal age $\geq$ 35 years, body mass index > 30 kg/m^2, and stage 1 or 2 hypertension by systolic blood pressure (> 130 mmHg or > 140 mmHg respectively). Chronicity of chronic hypertension was a variable without a known specific clinical threshold of significance. To investigate for a threshold of significance, stratified analysis was undertaken by quartiles of hypertension chronicity.

6.4 RESULTS

In a database of 43,910 deliveries, 233 births occurred in 186 women with chronic hypertension. Prevalence of chronic hypertension was 0.55%. Preeclampsia occurred in 36 (15.5%) of these births, of which 19 (8.2%) had severe features.

Non-modifiable risk factors associated with risk of preeclampsia on univariable analysis were: previous preeclampsia (OR 5.5 95%CI 1.9-15.7), being born overseas (OR 2.8 95%CI 1.3-5.8) and hypertension chronicity >5 years (OR 2.7 95%CI 1.2-6.3). After adjusting for site, age, parity, BMI, and renal disease, hypertension duration >5 years and previous preeclampsia remained independent risk factors (Table 6.2).

A large number of potentially modifiable risk factors for preeclampsia were evaluated, however there was no statistically significant association with superimposed preeclampsia (Table 6.3).

6.5 DISCUSSION

This study has demonstrated that superimposed preeclampsia is highly prevalent in a local population of women with chronic maternal hypertension. The use of clinical risk factors present from early pregnancy to predict risk of superimposed preeclampsia was explored, and a number of historical non-modifiable risk factors posed the highest risk. An additional important observation was that over the study period, aspirin use to reduce preeclampsia risk in these high-risk women was low.

Incidence of preeclampsia in this study was high at 15.5%. This rate is higher than the incidence of preeclampsia observed in Chapter 5 of 13.3%. Explanation for this observation relates to the differing methodologies used for preeclampsia diagnosis ascertainment between studies. This study utilised manual medical record review by two reviewers, whereas Chapter 5 utilised the obstetric birth database only. Reduced sensitivity of this obstetric birth database for preeclampsia diagnosis was also observed in Chapter 3, and has also been described elsewhere regarding similar state-based and national birth databases (48, 175).

An unexpected observation was the association between being born overseas and risk of superimposed preeclampsia in univariable regression analysis. Migrants to Australia are recognised to have increased pregnancy morbidity, although this is not specific to the development of preeclampsia (276). This is thought to be due to a number of factors such as late pregnancy booking, communication difficulties and poor health literacy due to language barriers, and social isolation. Being born overseas may also be a potential surrogate marker for ethnicity, as women born overseas may be from more ethnically diverse backgrounds than those born in Australia. Ethnicity is an important risk factor for the development of preeclamspia worldwide. However, ethnicity was not measured in this analysis as this metric was missing in 68% of medical records. Country of birth was documented in 96% of medical records. The association between country of birth and preeclampsia did not persist after adjustment for potential confounders, suggesting other factors may be influencing the association within this cohort.

A past history of preeclampsia was demonstrated to be a strong and independent risk factor for superimposed preeclampsia in this study. This observation has also been made by Chappell et al. 2008, Sibai et al. 1998, and Lercarpentier et al. 2013, with varying degrees in the strength of association. Interestingly, Sibai et al. 2011 published an alternative study which did not support this association. Reasons for this difference are unclear, however a lack of adjustment for underlying chronic renal disease and body mass index in earlier studies are proposed by authors as a possible explanation. That being said, this current study adjusted for these significant confounders, and the association between previous preeclampsia and risk of superimposed preeclampsia persisted.

Risk factors relating to the potential severity of chronic maternal hypertension were thoroughly examined in this study. Interestingly, chronicity of hypertension specifically for greater than 5 years was associated with risk of superimposed preeclampsia. Other metrics including antihypertensive use, number of antihypertensives used, blood pressure control at pregnancy booking, and presence of secondary hypertension did not show an association. Mechanistically, it is possible that women with a longer duration of chronic hypertension have a higher degree of established vascular remodelling. This vascular remodelling may lead to failure of the physiological flexibility required for

optimal placentation in early pregnancy, thus increasing risk of subsequent preeclampsia.

Others researchers have examined the association between chronicity of hypertension and risk of superimposed preeclampsia. Sibai et al. 1998 observed that women with chronic hypertension had the highest risk of superimposed preeclampsia if both hypertension had been present for at least 4 years, and proteinuria was present in first trimester. The presence of early pregnancy proteinuria suggests this observation may be confounded by coexisting chronic kidney disease. Lecarpentier et al. also evaluated duration of hypertension and preeclampsia risk in a cohort of women with essential hypertension. The threshold of 4 years was also used in this study and an association was not demonstrated. Authors did not indicate a rationale for dichotomising hypertension chronicity at this point.

Aspirin use was low and was not associated with reduced preeclampsia risk in this study. Although the lack of observed benefit in this study may simply be a reflection of low aspirin usage, there has been recent question regarding benefit across the spectrum of chronic maternal hypertension. Specifically, certain subpopulations are demonstrated to have greater benefit than others. Subgroup analysis of the ASPRE and MFMU trials observed that women with chronic hypertension may have greater benefit from aspirin at reducing risk of term, rather than preterm preeclampsia (277, 278). Importantly, both studies utilised differing aspirin doses, provided no information on the severity or chronicity of hypertension, and were of relatively small sample size.

Although not a study specifically evaluating preeclampsia risk with chronic maternal hypertension, Hausperg et al. provided additional insight into the interaction between hypertension and aspirin benefit to reduce preeclampsia risk (279). Women at high risk of preeclampsia (chronic hypertension, previous preeclampsia, diabetes, and twin pregnancy) were recruited to a placebo-controlled trial investigating benefit of aspirin to reduce preeclampsia risk. Secondary analysis of women with either diabetes or previous preeclampsia was performed evaluating aspirin use and preeclampsia risk with stratification by blood pressure at study enrolment in early pregnancy. A significantly higher risk of preeclampsia was seen in women with stage 1 hypertension (BP > 130/80

mmHg) as compared to normotensive women in the placebo arm. In the aspirin intervention arm, women with stage 1 hypertension had dramatic reduction in preeclampsia risk as compared to normotensive women. Although women with chronic hypertension were excluded from analysis, elevated blood pressure in the first half of pregnancy in this study suggests possible underlying chronic hypertension. Pre-pregnancy blood pressures were not available for confirmation however.

Considering these studies demonstrating mixed aspirin benefit in women with hypertension, it could be hypothesised that aspirin may be of greater benefit in those with 'milder' chronic hypertension. Women with abnormal but less well-established vascular remodelling due to chronic hypertension may potentially demonstrate greater pharmacological response to aspirin. Others have attempted to examine this concept by observing aspirin benefit in women considered to have 'milder' chronic hypertension, characterised by a normal blood pressure in early pregnancy. However, conclusions were unable to be made due to low use of aspirin (272).

The inconsistencies from these studies highlight that there are likely many pathways to developing preeclampsia for women with chronic hypertension. Given the well-established safety profile of aspirin, widespread rather than restricted use in women with chronic hypertension is likely provide benefit rather than harm, even it benefit is only modest.

Relative strengths of this study are that although this was a retrospective cohort study, internal validity was enhanced by the use of two reviews, one of which was blinded to preeclampsia status to reduce unconscious bias. Other strengths are the efforts taken to adjust for potential confounders, and novelty/originality of the possible risk factors evaluated for superimposed preeclampsia.

Limitations of this study are mainly related to sample size. Due to the rarity of chronic maternal hypertension, only a small number of cases were available from almost 50,000 birth records over ten years. A small sample size reduced study power and subsequent ability to draw strong conclusions from the observed associations. Due to the nature of the variables of interest and the requirement for detailed medical record review to obtain them, this type of exploratory analysis would not be possible using population or

registry data. At the very least, this study is hypothesis-generating for design of future prospective studies where highly-relevant variables such as blood pressure control and type of antihypertensive used could be further explored.

An important final limitation to discuss is the acknowledgement that reporting bias may cause overestimation in the morbidity of chronic hypertension in pregnancy. Chronic maternal hypertension is known to be underreported, and it is highly probable that those experiencing increased morbidity may be a subgroup with phenotypically severe disease, and be more likely to have both their hypertension and complications reported. Women with chronic hypertension in pregnancy are more likely to have hypertension documented in their medical record if they are taking antihypertensives, or if they have chronic hypertension over multiple hospital admissions (48). These characteristics are potential markers of more severe disease. Reflection on these aspects is important when considering the high prevalence of postpartum hypertension seen in Chapter 3 and Chapter 4. It is possible that unrestricted application of morbidity rates derived from a more phenotypically severe group may cause risk overestimation, and highlights the need for ongoing research in this area.

6.6 CONCLUSION

Baseline risk of preeclampsia is high in women with chronic hypertension. In this study, additional historical risk factors such as previous preeclampsia and a longer duration of chronic hypertension posed the highest additional risk for developing superimposed preeclampsia. These risk factors are non-modifiable and historical, and are present prior to conception which presents opportunity for pre-pregnancy counselling. This study also highlights the importance careful clinical appraisal in early pregnancy in women with chronic hypertension to best direct appropriate gestational management.

6.7 ACKNOWLEDGEMENTS

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Table 6.1 Risk factors of interest

Non-modifiable risk factors	Potentially modifiable risk factors
Age	Body mass index
Parity	Smoking
Multiple gestation	Aspirin use before 16 weeks
Previous preeclampsia	Gestation at pregnancy booking visit
Country of birth	Blood pressure at booking visit
Chronic kidney disease	Systolic blood pressure
Pre-existing diabetes	Diastolic blood pressure
Duration of chronic hypertension (years)	Mean arterial pressure
Secondary hypertension	Antihypertensive use
Assisted reproductive technology	At conception
	In first trimester
	Number of antihypertensive used

Table 6.2 Maternal outcomes associated with chronic hypertension

	No preeclampsia	Preeclampsia	Unadjusted OR	Adjusted OR
n	197 (84.6%)	36 (15.5%)		
Non-modifiable risk factors				
Age (years)	35 [30, 38]	33 [30, 38.5]	-	-
Age ≥ 35 years	100 (50.7%)	14 (38.9%)	0.6 (0.3-1.3)	-
Nulliparity	74 (37.5%)	19 (52.8%)	1.9 (0.9-3.9)	2.2 (1.0-89.1)
Previous preeclampsia	33/123 (26.8%)	12/17 (70.6%)	5.5 (1.9-15.7)	7.1 (2.1-24.6)
Born overseas	44 (22.3%)	16 (44.4%)	2.8 (1.3-5.8)	2.4 (0.5-11.1)
Chronic diabetes	10 (5.1%)	2 (5.6%)	1.1 (0.2-5.4)	-
Chronic kidney disease	21 (10.6%)	8 (22.2%)	2.4 (0.9-5.9)	0.9 (0.1-6.5)
Duration of chronic hypertension	3 [1.5, 7]	6 [2, 10]	-	-
Hypertension duration > 5 years	65/164 (39.6%)	13/23 (56.5%)	2.7 (1.2-6.3)	9.6 (1.7-46.1)
Secondary hypertension	19/83 (22.9%)	6/24 (25.0%)	1.4 (0.5-4.5)	-

Prevalence (%) and median [IQR]. Denominator specified when data incomplete for variable. Adjusted odds ratio (OR) – adjusted for site, age, parity, BMI, and renal disease.

Table 6.3 Potentially modifiable risk factors for preeclampsia

	No preeclampsia	Preeclampsia	Unadjusted OR	Adjusted OR
n	197 (84.6%)	36 (15.5%)		
Potentially modifiable risk factors				
Smoking	14/197 (7.1%)	2/26 (7.7%)	0.8 (0.2-3.5)	-
Gestation at booking visit	13 [10, 14]	13 [10, 14]	-	-
Aspirin use before 16 weeks	29/183 (15.8%)	9/35 (25.7%)	1.8 (0.8-4.2)	2.1 (0.6-6.7)
Body mass index				
Body mass index (BMI)	31 [26, 14]	27.5 [25, 33]	-	-
BMI ≥ 30 kg/m^2	84 (42.6%)	21 (58.3%)	1.9 (0.9-3.8)	1.1 (0.3-3.4)
BMI ≥ 35 kg/m^2	73 (37.1%)	8 (22.2%)	0.5 (0.2-1.1)	0.9 (0.3-3.2)
Antihypertensive use				
Use at conception	102/170 (79.6%)	18/33 (54.5%)	1.3 (0.6-2.6)	0.9 (0.3-2.9)
Use in first trimester	74/170 (43.5%)	8/33 (24.2%)	0.9 (0.6-2.4)	-
Use of ≥ 2 antihypertensives	10/170 (5.9%)	2/33 (6.1%)	0.7 (0.3-4.1)	-
Blood pressure (BP)				
Systolic BP at booking (mmHg)	130 [120, 140]	135 [130, 145]	-	-
Systolic BP ≥ 130 mmHg	99/159 (62.2%)	25/31 (80.6%)	2.6 (1.0-6.6)	4.9 (0.9-27.1)
Systolic BP ≥ 140 mmHg	51/159 (32.1%)	12/31 (38.7%)	1.3 (0.7-3.0)	-
Diastolic BP at booking (mmHg)	80 [75, 88]	85 [80, 90]	-	-
Diastolic BP ≥ 80 mmHg	109/159 (68.5%)	24/31 (77.4%)	1.6 (0.6-3.9)	-
Diastolic BP ≥ 90 mmHg	36/159 (22.6%)	11/31 (35.5%)	1.9 (0.8-4.3)	-
Mean arterial pressure (mmHg)	98 [93,103]	102 [93, 108]	-	-
MAP at booking ≥ 95 mmHg	84/159 (52.8%)	20/31 (64.5%)	1.8 (0.8-4.1)	-

Prevalence (%) and median [IQR]. Denominator specified when data incomplete for variable. Adjusted odds ratio (OR) – adjusted for site, age, parity, BMI, and renal disease.

Chapter 7

GENERAL DISCUSSION

7.1 GENERAL DISCUSSION AND IMPLICATIONS FOR PRACTICE

The links between hypertensive disorders of pregnancy and long term cardiovascular risk in women are no longer in doubt. However, the underlying mechanism and natural history of progression towards overt cardiovascular disease, and how to best screen, risk stratify, and potentially risk-modify or prevent disease remain unanswered questions.

The main aims of this thesis were to evaluate women after hypertensive pregnancy for both traditional and novel markers of cardiovascular risk and to explore for signs of subclinical vascular change. Detecting vascular dysfunction and change may enhance our understanding of mechanistic pathways and time-course towards development of clinically evident disease. Through a series of 5 studies, I have followed a path of inquiry to address my original aims, and evolved and answered new research questions along this path.

The NASCENT study of Chapter 3 demonstrated that many women have persisting uncontrolled masked or sustained hypertension at 6-12 months postpartum after hypertensive pregnancy. Potential contributing factors to the high prevalence of uncontrolled hypertension were investigated, and inaccurate birth medical records and poor rates of postpartum follow-up were observed to be possible factors. In addition to this, novel biomarkers of cardiovascular disease risk were explored, however no clear trends were observed within this cohort.

An original aim of this study was to *longitudinally* characterise both the development of cardiovascular risk factors and subclinical vascular changes in the postpartum period. Significant research attrition and slow recruitment greatly restricted the ability to collect valid longitudinal data using available resources within a reasonable timeframe, such that Chapter 3 is presented as a cross-sectional study.

Critical reflection on both the study design and cross-sectional research findings opened other avenues for inquiry. A number of key observations regarding the study population were made; (a) research participation is difficult for postpartum women, (b) postpartum women prioritise their children over personal aspects such as their own health, and (c)

follow-up rates after hypertensive pregnancy were poor and uncontrolled hypertension was prevalent.

Investigation of the literature into the health behaviours of postpartum women and strategies for follow-up after hypertensive pregnancy provided insight, and confirmed the observation of generally suboptimal postpartum participation in both research and intervention strategies such as specialised clinics. Postpartum women are strongly motivated by the needs and health of their children. Other researchers have observed that the approach of targeting an individuals' motivations rather than focussing on education alone is superior in improving adherence to recommendations in women's cardiovascular health (12). Combining these principles with the observation that the majority of health encounters for women in the first 6-months after childbirth are for their children and with a child health nurse, gave inspiration for the study design concept of Chapter 4 (238).

Chapter 4 demonstrated feasibility and proof-of-concept in utilising child health nurses to perform limited screening of maternal health to identify women who may benefit from further follow-up after diabetes or hypertension in pregnancy. Strengths of this approach were; (a) over 75% of *all* postpartum women residing in the catchment area were screened, (b) unrestricted screening for hypertension ensured all women received follow-up of blood pressure regardless of birth record documentation, previous treatment of blood pressure, or an individuals' understanding regarding need for follow-up, and (c) screening utilised a primary healthcare service already existing within current models of care. Additional findings of this study were that 1 in 10 of all women screened could benefit from further follow-up of either gestational diabetes or hypertension. This further confirms the findings of Chapter 3; that follow-up after pregnancy hypertension could be improved.

The observed high prevalence of postpartum hypertension in both Chapter 3 and Chapter 4 posed questions regarding the morbidity of chronic hypertension in pregnancy, as many study participants were either planning pregnancy or pregnant at the time of enrolment. A paucity of literature relevant to the local population limited ability to provide accurate counselling and risk assessment to women regarding risk of

adverse pregnancy outcomes. As such, Chapter 5 explored the pregnancy morbidity associated with chronic maternal hypertension in a large cohort of local women after adjusting for baseline maternal characteristics which may confound interpretation of findings. Observations were consistent with other published cohorts demonstrating significant maternal and neonatal morbidity as compared to normotensive women, and a high rate of superimposed preeclampsia (46, 176, 178, 275).

Chapter 6 further investigated the associations between chronic hypertension and risk of superimposed preeclampsia. Evaluation was focussed on non-modifiable and potentially modifiable clinical risk factors easily-identifiable at the pregnancy booking visit which did not require additional investigation or testing. The strongest risk factors for superimposed preeclampsia were a previous history of preeclampsia and chronicity of hypertension greater than 5 years. These risk factors are historical and non-modifiable. Knowledge of these additional risk factors in women with chronic hypertension presents opportunity for pre-conception counselling and early pregnancy risk-stratification to best direct appropriate gestational management.

A dominant finding of this thesis was that persisting postpartum hypertensive abnormalities were prevalent across the full spectrum of hypertensive disorders of pregnancy. Within Australia, follow-up of all women is recommended after hypertensive pregnancy. However, formalised postpartum follow-up with an obstetrician or other specialist is often restricted to women whom experienced significant morbidity such as preterm delivery or preeclampsia with severe features. While this seems prudent when considering allocation of resources to benefit those at highest risk, other women with milder presentations are referred to their general practitioner for follow-up. Major limitations of this follow-up pathway are that onus for seeking follow-up lies with the individual, and that important persistent abnormalities requiring management after hypertensive pregnancy such as persisting proteinuria or hypertension are frequently asymptomatic.

Other studies have explored the development of cardiovascular risk factors across the full spectrum of hypertension in pregnancy in the first few years after delivery. Findings from the Nurses' Health Study II suggest that risk of being diagnosed with chronic

hypertension after hypertensive pregnancy is highest in the first 5 years after delivery as compared with later in life (3). Importantly, women in this study who experienced gestational hypertension had a similar risk and timeline to developing hypertension and other cardiovascular risk factors as women after preeclampsia. This observation combined with the findings in Chapter 3 and the recognised pitfalls of relying on pregnancy medical records to correctly distinguish between preeclampsia and gestational hypertension, suggest a more inclusive and generalised approach to maternal follow-up after hypertensive pregnancy may be justified (175, 280).

The identification of chronic hypertension in young women is important as there are implications for both short and long-term health. Identification allows for investigation of secondary causes of hypertension and opportunity for further management. Although hypertension in young adulthood is associated with increased risk of later-life cardiovascular disease, optimal long term management of blood pressure to modify risk remains uncertain as longitudinal interventional data is lacking (59). Due to the likely significant time-delay between risk factor identification and cardiovascular events in this population, as expressed eloquently by another researcher; “the challenges of conducting such research are formidable” (125). Nonetheless, blood pressure is observed in other populations to have a continuous positive correlation with cardiovascular risk down to normotensive levels, and so it is probable that any degree of blood pressure reduction may be of benefit.

While clear evidence-based treatment guidelines for hypertension therapy in young women may not yet exist, dismissiveness towards management based on low calculated absolute cardiovascular risk using risk estimation tools seems a somewhat unidimensional approach. This is especially important when considering the potential morbidity of chronic hypertension at a younger age which may manifest in pregnancy. Although blood pressure modification either before or during early pregnancy has not yet been demonstrated to impact pregnancy outcome, other therapies such as aspirin, exercise, or weight reduction in obese women may reduce pregnancy morbidity (208, 209, 260, 277). Lifestyle interventions during the inter-pregnancy period to improve blood pressure and other health parameters may possibly reduce future health risks and

are unlikely to cause harm, however are not currently supported by a strong evidence base (281).

This thesis also importantly demonstrated that follow-up after pregnancy hypertension and gestational diabetes was suboptimal and could be improved. This theme was carried from Chapter 3 and explored in more detail in Chapter 4. Key findings potentially impacting follow-up were; (a) attendance for routine postpartum medical assessment was unreliable, (b) inclusion of a blood pressure check during medical review was inconsistent, and (c) birth medical records displayed reduced accuracy for key outcomes such as presence of preeclampsia. There are likely many factors impacting whether an individual seeks or attends follow-up, and the crucial role of the general practitioner in longitudinal care and health education around time of delivery were not explored in this thesis.

It is highly probable moving forward that improvement in postpartum follow-up will require a multidisciplinary approach which recognises and addresses the importance of transition; from obstetric care to primary health care, and from pregnancy to parenthood. The development of postpartum care guidelines for women after hypertension in pregnancy will provide clarity regarding recommendations during this time of transition, however ongoing in research in this area is necessary to support evidence-based practice.

Finally, hypertension in pregnancy gives poise to adopt the 'life course approach' to health; that key stages in life present opportunity to prevent and control disease (282). Hypertension in pregnancy identifies women with a high-risk phenotype, thus enabling potential for timely intervention to modify future risk. How best to modify future disease risk remains currently unanswered, however lifestyle interventions to manage and prevent development of non-communicable diseases will likely be of benefit and have desirable transgenerational effects for offspring.

7.2 LIMITATIONS AND FUTURE DIRECTION

A significant limitation of this work is an absence of longitudinal data. This is particularly relevant to the findings of Chapter 3. The natural history of progression and potential resolution of hypertensive phenotypes in the postpartum period is not well studied and is a limitation of other published works in this area. Poor understanding of the relationship to future cardiovascular events and time-course to developing cardiovascular risk factors limit both use of targeted screening and design of future studies to determine optimal long term management. Further work is needed to examine these factors. Considerate study design to accommodate the unique characteristics of this study population will be required.

The findings of Chapter 4 outlined a feasible and pragmatic approach to improving follow-up after hypertension and diabetes in pregnancy. It also demonstrated a potential for improved maternal research participation through utilisation of maternal and child health services. Although a number of barriers to wider implementation of maternal health screening were identified in qualitative analysis, these barriers were felt to be easily surmountable by both myself and participating maternal and child health nurses. Importantly, Chapter 4 did not explore effectiveness of health screening in ensuring formal follow-up occurs, or whether screening provides benefit to overall maternal health. These will be essential aspects to address with future research.

While nurse-initiated health screening is not a new concept, to date, I have not found evidence of this approach being utilised elsewhere to improve postpartum follow-up after complicated pregnancies. This poses exciting opportunity to not only consider wider implementation of maternal health screening, but to explore avenues for longitudinal observation and lifestyle interventions in postpartum women. Varying models of child and family healthcare exist worldwide, however many countries in both the developed and developing world similarly utilise primary care nurses in this role. Wider application of this concept could be considered internationally for the promotion of maternal follow-up after medical complications in pregnancy through child and family health nurses.

The findings and original contributions of Chapter 5 in particular are limited by sample size. Although Chapter 5 successfully outlined pregnancy outcomes associated with chronic hypertension in a local population, a more enhanced understanding of these associations would likely occur if population data with longitudinal linkage of multiple datasets was utilised. Significant efforts were made to obtain linked population datasets within the timeframe of this thesis, however was ultimately not achievable.

Benefits of longitudinal linkage in this manner overcome many of the shortcomings of existing published population data in estimating disease prevalence and associated morbidity (48). Specific linkage of the state birth record database (Victorian Perinatal Data Collection) and the hospital admission database (Victorian Admitted Episode Database) is planned to link birth episodes to antenatal or postnatal admissions to enhance identification of early postpartum pregnancy complications and maternal comorbidities.

Currently, there is no published population data in Australia which captures early postpartum maternal morbidity related to hypertension which occurs *after* discharge or transfer from the hospital in which birth occurs. This would be important to explore as highlighted by the observation in Chapter 3; that 9 of the 57 women with hypertension in pregnancy were readmitted to hospital after discharge post-birth for further management of severe hypertension including preeclampsia. I hypothesise that longitudinal linkage of these datasets not only to postpartum events, but also to other pregnancy episodes may provide further insight into understanding the interaction between hypertension in pregnancy and chronic maternal hypertension throughout the reproductive years.

7.3 CONCLUSIONS

This thesis provides insight into how hypertensive disorders of pregnancy may be linked to future cardiovascular disease through exploring the significance of chronic hypertension before pregnancy, and assessing vascular function and cardiovascular risk factors after preeclampsia. Additionally, strategies to improve identification of hypertension after pregnancy through nurse-initiated health screening were evaluated.

A summary of the main findings of this thesis is as follows:

1. Hypertensive phenotypes were common amongst women not previously known to have chronic hypertension 6-12 months after hypertensive pregnancy
2. Masked hypertension was frequently observed after hypertensive pregnancy. Although ABPM is required for diagnosis, stage 1 hypertension on office blood pressure measurement proved a strong predictor for masked hypertension
3. Biomarkers for vascular dysfunction and cardiovascular risk such as microalbuminuria and novel markers for endothelial dysfunction were not shown to vary between women with a history of normotensive or hypertensive pregnancy
4. Obesity was strongly associated with gestational hypertension in a local population, highlighting potential for postpartum lifestyle intervention to improve health
5. Chronic hypertension was demonstrated to correlate with significantly increased pregnancy morbidity in a population of local women
6. Chronicity of hypertension and previous preeclamptic pregnancy were the strongest independent risk factors for superimposed preeclampsia in women with chronic hypertension
7. Follow-up after hypertension in pregnancy is suboptimal, and postpartum nurse-initiated maternal health screening is feasible in identifying women who may benefit from further care
8. Postpartum research participation may be enhanced by incorporating research into routine care pathways, particularly care relating to child health and development

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