MONASH University

Understanding management of hypertensive disorders of pregnancy and medication use during pregnancy: A mixed methods approach

Amyna Helou

BPharm (Hons), GradCert PharmPrac

A thesis for submitted for the degree of

Doctor of Philosophy

at Monash University in 2021

Centre for Medicine Use and Safety

Faculty of Pharmacy and Pharmaceutical Sciences

Melbourne, Australia

By time,

Indeed, mankind is in loss,

Except for those who have believed

and done righteous deeds

and advised each other to truth

and advised each other to patience.

The Holy Quran: Chapter 103 Verses 1-3

This thesis is dedicated to my family

For their endless prayers, love and encouragement

Copyright notice

Table of contents

Acknowledgements

My PhD candidature has been a remarkable experience and would not have been possible without the assistance, support and patience of my supervisors, collaborators, colleagues, friends and family.

To my supervisors **Dr Johnson George** and **A/Prof Kay Stewart**, thank you both for giving me the opportunity to find my place as a researcher. I could not have done this without you both. It has been a pleasure to work with you.

To **Johnson**, thank you for your support throughout my candidature. Thank you for staying with me until the end despite your increased responsibilities. Your advice, guidance and assistance are much appreciated.

To **Kay**, thank you for staying with me until the end despite your retirement from full university duties. I greatly appreciate the precious time that you put towards assisting me to completion. Thank you for your support and for believing in me. Your advice, guidance and encouragement were instrumental to my progress at all times.

To my collaborators **A/Prof Kath Ryan** and **Prof Susan Walker**, thank you both for your expertise, guidance and support in preparing the manuscripts. It has been a pleasure working with you.

Thank you to my panel members **Prof Simon Bell, Prof Phillip Thompson** and **A/Prof Jennifer Marriot** for your advice and encouragement at my final PhD seminar. I also thank **Prof Roger Nation** and **Prof Lisa Amir** for their input and encouragement earlier in my candidature.

I thank all of the past and present academic staff members of the Faculty of Pharmacy and Pharmaceutical Sciences who assisted me in my journey. Special gratitude to **Jenny McDowell, Janet Leeder, Safeera Hussainy, Tina Brock, Jenni Ilomaki** and **Liz Morabito** for their support. I would also like to thank **Carolyn Fox**, **Karen Drakatos, Gaby Bright** and the team at the **Monash**

Graduate Research Office for their assistance and support during my candidature. My gratitude is also owed to my faculty for their support, especially during the recent pandemic.

My gratitude also extends to **Maxine Cuskelly** from CL Butchers Library for her support and encouragement throughout my candidature. Thank you also to **Stephanie Jury** and **Mina Nichols-Boyd** for their assistance. I also thank the team at the Hargrave-Andrews and Matheson Libraries at Clayton campus for their support during my time in the PhD hub at Monash Clayton.

Thank you to PhD students, past and present, at the Centre for Medicine Use and Safety for your friendship and encouragement. Special thank you to **Elida**, **Siow Chin, Angelina, Cikie**, **Agnes**, **Ching Jou, Clare**, **Julia**, **Paulina**, **Souheila**, **Leslie**, **Kate** and **Leonie**.

I would also like to acknowledge my closest friends for their support and encouragement. Thank you for being there for me even when I did not know that I needed it.

Most importantly, I would also like to thank my family for their unconditional love, prayers and support. I hope that I have made you all proud. To my wonderful parents, thank you for believing in me and for your endless prayers and unwavering support. Thank you for always encouraging me to better myself, aim high and follow my aspirations. To my beautiful siblings, Laila, Abdallah, Linah and Jalal, thank you for your prayers, encouragement and support. To my parents-in-law, thank you for your endless prayers and for checking up on me throughout this journey despite your situation in Syria. To my marvellous husband Ibrahim, thank you for standing by me through the ups and downs of this journey. No words can truly express my gratitude for the many sacrifices you made to allow me to reach this goal. I could not have done this without your love, encouragement and support. Thank you for being my best friend. To my precious daughter Safiyah and precious son Jameel, much love to you. Thank you for lighting up my way through this journey. I hope that my journey will be an inspiration for you to aim high and follow your dreams.

I would also like to acknowledge the struggle of the free Syrian people who are from the land that my family and I originate. From you I have gained inspiration and been taught about true resilience and perseverance.

Abstract

Background

Hypertensive disorders of pregnancy (HDP) complicate approximately 10% of pregnancies in Australia. HDP are a leading contributor to maternal and neonatal morbidity and mortality worldwide. Despite multiple national and international clinical guidelines for the management of HDP, controversies remain surrounding the blood pressure (BP) threshold for initiation of antihypertensive therapy in mild-moderate hypertension, the target diastolic BP and the timing of delivery in non-severe gestational or chronic hypertension. In-practice use of antihypertensive medication in this population has not been previously studied, neither from the system perspective nor that of the patient.

Aims and Objectives

The overall aim was to provide an understanding of management of HDP and medication use during pregnancy.

Specific objectives were to:

i. provide an understanding of the management of HDP in the Australian context by investigating compliance to Australian guidelines, specifically:
    a. thresholds for initiation of antihypertensive therapy;
    b. appropriateness of medication regimens; and
    c. use of aspirin in women with known risk factors for development of pre-eclampsia.
ii. estimate the rate of non-adherence to antihypertensive therapy during pregnancy;
iii. understand women's perspectives on adherence to medication and management of their HDP; and
iv. contextualise the women's perspectives via documentation of management and outcomes.

Methods and Key Findings

Phase 1 (Chapter 3): A retrospective review of medical records of women with HDP who gave birth in 2010 at one large Victorian tertiary maternity hospital, revealed that clinical guidelines were mainly being followed. Low dose aspirin for the prevention of pre-eclampsia, however, was often over-looked, resulting in a 12% uptake of timely prescription. Only 20% of women with HDP were prescribed an antihypertensive during pregnancy.

Phase 2a (Chapter 4): A cross-sectional survey of 100 pregnant women being treated with an antihypertensive for HDP found that nine in ten self-reported sub-optimal adherence to antihypertensive medication. Factors associated with non-adherence were confusion about antihypertensive medication and making changes to recommended medication management to suit their lifestyle or according to how they were feeling**.** A potential role for pharmacists in the optimisation of medication adherence during pregnancy was identified.

Phase 2b (Chapters 5 & 6): In-depth interviews of a subsample of 27 women provided a unique perspective on medication use, adherence and clinical management of HDP from the pregnant women's view. Adherence to antihypertensives during pregnancy is influenced by the women's understanding of risks. Demonstration of gaps in clinical management from the women's perspective informed the need to include the patient's view in the management of HDP. Roles for community pharmacists were identified in optimisation of medication adherence, education of women of reproductive age with chronic hypertension, and assistance with BP monitoring during pregnancy and in the long-term postpartum period.

Phase 2c (Chapter 7): A prospective follow-up study, via review of medical records, of management and outcomes in the total cohort consolidated the findings of phases 2a and 2b and contextualised the women's perspectives. Clinical guidelines were mainly followed. There was, however, a greater chance of developing severe hypertension, if the initial antenatal visit was after 12 weeks gestation. Moreover, there were some delays in switching antihypertensive to a safer pregnancy alternative.

Conclusions

Gaps exist in clinical management of pregnant women with HDP, both in primary healthcare provided by GPs and pharmacists in the pre-conception and postpartum periods, and in the maternity antenatal hospital health system. Community pharmacists are in an ideal position as front-line healthcare professionals to initiate conversations with women of child-bearing age treated using antihypertensives regarding timely switching to agents that are safer in pregnancy. Hospitals should ensure that women with chronic hypertension have their first antenatal hospital appointment by 12 weeks gestation to allow consultation regarding potential risks of pregnancy, timely prescription of low dose aspirin for the prevention of pre-eclampsia, and close monitoring of HDP and fetal wellbeing throughout the pregnancy. Moreover, women with gestational hypertension or pre-eclampsia during pregnancy should be informed of the potential for future cardiovascular risks, and plans for BP follow up postpartum should be made in collaboration with GPs and community pharmacists. Finally, models of care including obstetricians, midwives, GPs and pharmacists as well as empowerment of all women with HDP to take an active role in their cardiovascular health can potentially improve their health outcomes and those of their offspring.

Publications and presentations during enrolment

Publications included in this thesis

Helou A, Walker S, Stewart K, George J. *Management of pregnancies complicated by hypertensive disorders of pregnancy: Could we do better?* Australia and New Zealand Journal of Obstetrics and Gynaecology. 2017;**57**(3): 253-259. https://doi.org/10.1111/ajo.12499.

Helou A, Stewart K., George J. *Adherence to anti-hypertensive medication in pregnancy*. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2021;**25**:230-24. https://doi.org/10.1016/j.preghy.2021.06.002.

Helou A, Stewart K, Ryan K, George J. *'I wish my body was stronger': A qualitative study of attitudes and behaviours regarding treatment of hypertensive disorders of pregnancy*. SAGE Open Medicine. 2021;**9**:1–10. https://doi.org/10.1177/20503121211032480.

Helou A, Stewart K, Ryan K, George J. Pregnant women's experiences with the management of hypertensive disorders of pregnancy. BMC Health Services Research. 2021;**21:**1292. https://doi.org/10.1186/s12913-021-07320-4.

Under Review

Helou A, Stewart K, George J. *Management of hypertensive disorders of pregnancy in two Australian tertiary care maternity hospitals***.** Obstetric Medicine

Conference presentations

Helou A, Stewart K, George J. *Treatment of high blood pressure in pregnant women attending an Australian maternity hospital*. Australasian Pharmaceutical Science Association Conference, Sydney, Australia (December 2012). Oral Presentation.

Helou A, Stewart K, George J. *Use of antihypertensives during Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women*. 1st Victorian Allied Health Conference, Melbourne, Australia (March 2014). Oral Presentation.

Helou A, Stewart K, George J. *Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women*. Australian Diabetes In Pregnancy Society-Society of Obstetric Medicine of Australia and New Zealand Joint Scientific Meeting, Queenstown, New Zealand (July 2014). Oral Presentation.

Helou A, Stewart K, George J. *Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women*. 9th Annual Monash University Post Graduate Symposium, Melbourne, Australia (November 2014). Oral Presentation.

List of tables

List of figures

List of abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ACOG	American College of Obstetricians and Gynecologists
ADEC	Australian Drug Evaluation Committee
BMC	BioMed Central
BP	Blood Pressure
CH	Chronic Hypertension
CMI	Consumer Medicines Information
CVD	Cardiovascular disease
DBP	Diastolic Blood Pressure
FDA	Food and Drug Administration
FGR	Fetal Growth Restriction
GH	Gestational Hypertension
GP	General Practitioner
HCP	Healthcare Professional
HELLP	Haemolysis Elevated Liver enzymes Low Platelet count syndrome
HDP	Hypertensive disorders of pregnancy
ISSHP	International Society for the Study of Hypertension in Pregnancy
IUGR	Intra-uterine Growth Restriction
IOL	Induction of Labour
NICE	National Institute for Health and Care Excellence
PE	Pre-eclampsia
SBP	Systolic Blood Pressure
SGA	Small-for-gestational age
SMBP	Self-monitoring of Blood Pressure
SOGC	Society of Obstetricians and Gynaecologists of Canada
SOMANZ	Society of Obstetric Medicine of Australia and New Zealand
SPSS®	Statistical Package for Social Sciences
TABS	Tool for Adherence and Behaviour Screening
TGA	Therapeutic Goods Administration

UK	United Kingdom
US	United States
WCH	White coat hypertension
WHO	World Health Organization

List of definitions

Fetus

An unborn baby from the eighth week after fertilisation until delivery.

Fetal Growth Restriction

A fetus born with a weight that is less than the 10th centile.

Gestational age

The age of the fetus measured from the first day of the mother's last menstrual period; an average pregnancy lasts 280 days, or about 40 weeks, from that day.

Gestational week

The length of the pregnancy from the mother's last menstrual period to the time of measurement (in weeks).

Singleton pregnancy

A singleton intrauterine pregnancy is a normal pregnancy with one baby/fetus, developing in the uterus.

Obstetric Physician

Doctors who are trained in a sub-specialty of general internal medicine and obstetrics that specialises in the process of prevention, diagnosing and treating medical disorders in pregnant women including hypertensive disorders of pregnancy.

Thesis including published works declaration

I hereby declare that this thesis 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.

This thesis includes three original papers published in a peer reviewed journal and two manuscripts under review. The core theme of the thesis is the understanding of management and medication use in pregnant women who experience hypertensive disorders of pregnancy. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, Amyna Helou, working within the Centre for Medicine Use and Safety under the supervision of Dr Johnson George and A/Prof Kay Stewart.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 3, 4, 5, 6 and 7 my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*
3	*Management of pregnancies complicated by hypertensive disorders of pregnancy: Could we do better?*	Published	60% Conceptualisation, data collection, data analysis, writing first draft and finalising manuscript	1) S. Walker. 20%. Concept and design of the study, data interpretation, critical revision of manuscript. 2) K. Stewart.10%. Concept and design of the study, data analysis, critical revision of manuscript. 3) J. George.10%. Concept and design of the study, data analysis, critical revision of manuscript.
4	*Adherence to anti-hypertensive medication in pregnancy*	Published	70% Conceptualisation, data collection, data analysis and interpretation, writing first draft and finalising manuscript	1) K. Stewart.15%. Concept and design of the study, data interpretation, critical revision of manuscript. 2) J. George. 15%. Concept and design of the study, data interpretation, critical revision of manuscript.

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*
5	*'I wish my body was stronger': A qualitative study of attitudes and behaviors regarding treatment of hypertensive disorders of pregnancy*	Published	65% Conceptualisation, data collection, data analysis and interpretation, writing first draft and finalising manuscript	1) K. Stewart. 20%. Concept and design of the study, data analysis, data interpretation, critical revision of manuscript 2) K. Ryan.10%. Concept and design of the study, data interpretation, critical revision of manuscript. 3) J. George. 5%. Critical review of manuscript.
6	*Pregnant women's experiences with the management of hypertensive disorders of pregnancy: a qualitative study*	Published	65% Conceptualisation, data collection, data analysis and interpretation, writing first draft and finalising manuscript	1) K. Stewart. 20%. Concept and design of study, data analysis, data interpretation, critical revision of manuscript. 2) K. Ryan.10%. Concept and design of the study, data interpretation, critical revision of manuscript. 3) J. George. 5%. Critical review of manuscript.
7	*Management of hypertensive disorders of pregnancy in two Australian tertiary care maternity hospitals*	Under Review	75% Conceptualisation, data collection, data analysis, and interpretation, writing first draft and finalising manuscript	1) K. Stewart. 10%. Concept and design of the study, data interpretation, critical revision of manuscript. 2) J. George. 15%. Concept and design of the study, data analysis, data interpretation, critical revision of manuscript.

*No co-authors were Monash students.

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student name: Amyna Helou

Student signature: **Date:** 15/07/2021

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Dr Johnson George

Main **Supervisor signature:** **Date:** 15/07/2021

CHAPTER 1

GENERAL OVERVIEW

1.1 Introduction

This thesis describes research investigating the management of hypertensive disorders of pregnancy (HDP) and medication use by pregnant women. Research to date has focused on the clinical management of HDP; previously known as hypertension in pregnancy, as well as general medication use during pregnancy. There has been very little work that addresses the management of HDP or the use of antihypertensives during pregnancy from the point of view of the patient.

This introductory chapter provides general background information to the study topics and the study population.

1.2 The burden of hypertension

Hypertension, commonly known as high blood pressure, is a serious medical condition that can increase the risk of many diseases including that of the heart, kidneys and brain. The World Health Organization (WHO) estimates the global incidence of hypertension to be 1 in 4 among men and 1 in 5 among women, resulting in over one billion affected people worldwide (1). The 2017/18 Australian Institute of Health and Welfare National Health Survey estimated that just over 1 in 5 adults, totalling 4.3 million, had hypertension (blood pressure ≥140/90 mm Hg or were taking blood pressure medication) (2). Adult hypertension is diagnosed when the systolic blood pressure (BP) is ≥140 mmHg and/or the diastolic blood pressure is ≥90 mmHg on at least two separate occasions over at least two separate days (3).

Hypertension is known as the 'silent killer' due to the lack of immediate symptoms and is a leading cause of premature death worldwide (1). This has prompted calls to implement programs to prevent hypertension, to optimise management of the condition and to minimise end stage organ failure. Modifiable risk factors include unhealthy food choices (high in saturated fat and trans fats, excessive salt consumption and a low intake of fruits and vegetables), physical inactivity, being overweight or obese, and consumption of tobacco and alcohol. Many initiatives, both locally in Australia and worldwide, have targeted these modifiable risk factors to help ease the burden of hypertension. Non-

modifiable factors, including chronic kidney disease or congenital heart disease, can result in secondary hypertension.

Hypertension also impacts work productivity through days off work due to ill health and reduced efficiency (4). This has the potential to impose an economic burden on individuals, employers and governments through reduced earnings and tax revenue. The American Heart Association, for example, estimated US$3.9 billion was lost due to hypertension-related productivity loss in the United States in 2013 (4) whilst in Australia hypertension caused AUD$137.2 billion in lost gross domestic product over the working lifetime in 2019 (5). Amongst the population affected by chronic hypertension are women of child-bearing age, and these women will be discussed in the context of pregnancy in the coming sections.

1.3 Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HDP) affect about 10% of pregnancies in Australia (6) and is a leading cause of maternal mortality and stillbirths worldwide (7). It is estimated that 30,000 maternal and 500,000 perinatal deaths are attributed to HDP annually (8). Maternal complications include increased risk of caesarean delivery, stroke and potential damage to the hepatic and renal organs (6, 9). Perinatal risks of maternal hypertension are well documented and include an increased occurrence of premature birth, impaired intrauterine growth (IUGR), low birth weight and respiratory distress syndrome (6, 10). The legacy of IUGR is lifelong, with an increased risk of neonatal and childhood morbidity, and increased risk of adult diseases such as coronary heart disease, adult hypertension, type 2 diabetes and hypercholesterolemia later in life (11).

In a pregnancy that is not affected by HDP, BP usually decreases in early pregnancy and reaches its lowest point during the early part of the second trimester when the diastolic BP is, on average, 15 mmHg lower than the pre-pregnancy value (12). The BP then rises during the third trimester and reaches pre-pregnancy levels by term (12).

Hypertension in pregnancy is defined by the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) as systolic BP greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg. These measurements should be confirmed by repeated readings over several hours (6). This is also known as mild-moderate hypertension. Severe hypertension is defined as a systolic BP greater than or equal to 170 mmHg with or without diastolic BP greater than or equal to 110 mmHg.

There are three main subtypes of HDP (6):

- Chronic Hypertension: diagnosed either prior to pregnancy or before 20 weeks gestation. This can be either primary hypertension or secondary hypertension.

- Gestational Hypertension: diagnosed after 20 weeks gestation.

- Pre-eclampsia: a multi-organ gestational disorder involving hypertension that can occur as a stand-alone disorder or superimposed on chronic hypertension. This can be either mild or severe. HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome presents in a subset of women with severe pre-eclampsia with or without other pre-eclamptic features.

1.4 Therapy and management of hypertensive disorders of pregnancy

The aim of treatment of high BP during pregnancy is to reduce the impacts on the mother and fetus alike. The threshold to diagnose HDP is generally agreed upon, with some minor differences between international guidelines. There is general consensus on the threshold to urgently treat severe hypertension. There is however a controversy surrounding the threshold to treat mild-moderate hypertension (6). This was the subject of a large multi-centre international study called 'Control of Hypertension In Pregnancy Study' (CHIPS) which found no significant differences in the risk of pregnancy loss, high-level neonatal care or overall maternal complications between less-tight (target diastolic BP 100 mmHg) versus tight (target diastolic BP 85 mmHg) control of hypertension in pregnant women with mild-moderate gestational or chronic hypertension (13). Hence the decision to treat mild-moderate hypertension often relies on the judgement of the treating obstetrician or physician.

1.4.1 Antihypertensive therapy

The first line antihypertensive medications recommended for use according to the Australian guidelines (6) are methyldopa, labetalol and oxprenolol (oxprenolol has now been discontinued). Prazosin, nifedipine and hydralazine are second line agents and are usually used as add-on therapy or in cases where the first line agents are deemed unsuitable or ineffective (6).

Other medications used in the management of HDP include low-dose aspirin (85-100mg) administered daily from prior to 16 weeks gestation for the prevention of pre-eclampsia in those at high risk (6, 14), such as those who have had pre-eclampsia in a previous pregnancy and those who have chronic hypertension. (6, 14) Calcium (1.5g/day) is also used for the prevention of pre-eclampsia, particularly in women who lack dietary calcium (6, 15).

A key to the optimal management of HDP is close monitoring of BP throughout the pregnancy to ensure adequate BP control and detect signs of pre-eclampsia.

1.5 Medication use and challenges during pregnancy

Prescribing medication for any condition during pregnancy involves an evaluation of the risk versus benefit balance by the prescriber (16). Potential harms of using antihypertensive medication during pregnancy may include increased risk of a small-for-gestational age neonate and congenital malformations (17). In Australia, the Australian Drug and Evaluation Committee (ADEC) has a classification of pregnancy (18). These classifications are explained in Table 1.1.

Table 1.1: Australian Drug and Evaluation Committee categorisation of risk of antihypertensives during pregnancy

Category	Definition	Antihypertensive
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.	Methyldopa
B1	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.	
B2	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.	Prazosin
B3	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.	
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful	Labetalol

Category	Definition	Antihypertensive
	effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.	Atenolol Nifedipine Hydralazine
D	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.	Angiotensin converting enzyme inhibitors (ACEIs) Angiotensin II receptor antagonists and renin inhibitors
X	Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.	

Despite methyldopa being the only antihypertensive medication with a category A pregnancy safety classification, labetatol, nifedipine, prazosin, hydralazine and oxprenolol (oxprenolol has now been discontinued) are also considered safe to be taken during pregnancy (6, 19). ACEIs and alpha-2 antagonists are commonly used antihypertensives in the general adult population but are not recommended in pregnancy (20). Similarly, beta-blockers, other than labetatol and oxprenolol, are also not recommended during pregnancy (17). It is important to note that the value of these categorisations has been questioned over the last decade (21,22).

Similarily, the consumer medicine information leaflets of antihypertensives such as labetalol and nifedipine contain the warning 'Do not take this medicine if you are pregnant (23,24). The examples of the CMIs of labetalol and nifedipine indicate that the labelling of medication use in pregnancy is worthy of an overhaul as suggested by Kennedy in 2011 (21). Despite the work of Kennedy, Hotham and others, (21,22) there has not been a substantial change in the labeling of medications for use in pregnancy in Australia yet. In the United States, the FDA is replacing pregnancy categories in CMIs with more useful information (25):

Pregnancy (includes Labor and Delivery):

- Pregnancy Exposure Registry
- Risk Summary
- Clinical Considerations

- Data

The labelling of antihypertensive medications used during pregnancy should follow safety data from evidence-based systematic reviews such as those by Abalos et al mentioned in section 2.8.

1.6 Adherence to treatment, predictors and measurements

The last few decades have witnessed intensive clinical and research interest in medication taking (26). Despite this, pregnant women are often excluded from such trials and hence minimal research exists about this important subset of the adult population. Moreover, health beliefs surrounding medication use in the general population are more powerful predictors of reported adherence than clinical and sociodemographic factors (27). Other aspects of medication use during pregnancy, including the perceptions and beliefs of pregnant women towards medication safety and risk, the impact of various sources of information on these perceptions and the general nature of use of medication during pregnancy have been widely explored (28-30). Only a limited number of studies have reported adherence to medication by pregnant women with pre-existing specific disease states, namely HIV-AIDs (31), Crohn's disease (32), ulcerative colitis (33), asthma (34) and hypothyroidism (35). No previous reports have been published about the self-reported adherence of pregnant women to medication in hypertensive disorders of pregnancy. One study by Webster et al (36) quantified the adherence of pregnant women who were taking labetalol or nifedipine for chronic hypertension during pregnancy by measuring urinary metabolites and reported an 88% adherence rate. This was, however, part of a randomised controlled trial comparing the two antihypertensives with ongoing monitoring of adherence and does not reflect real life behaviour. The WHO publication 'Adherence to Long-term Therapies: Evidence for Action', described the impact of five main factors that influence adherence to medication in the general adult population, namely: patient, socioeconomic characteristics, health condition, therapy and healthcare team/healthcare system (37). The nature of nonadherence has also been discussed in the literature. Intentional or intelligent nonadherence is rooted in the concept of the patient rejecting either the doctor's diagnosis or the prescribed treatment (38). Intentional adherence involves a patient altering their dosage regimen to suit their own needs (39). Fears or concerns about potential medication adverse effects and making changes to the recommended medication regimen to suit lifestyle are published examples of intentional nonadherence (34, 35). Hence, this is associated with their beliefs about the medication and involves a 'decision balance' (39). Unintentional nonadherence includes the patient forgetting to take the medication and confusion about the medication (35). Wroe studied the adherence of a cohort of COPD patients to inhaled corticosteroids

and found that unintentional nonadherence is less related to decision making and more associated with patient demographics, such as age (39). Hence, patient assessment of adherence should be able to distinguish between intentional and unintentional nonadherence to effectively tailor different interventions (37).

1.6.1 Assessment of patient adherence

Measurement of patient adherence is crucial for the efficient management of poor medication adherence. There is no 'gold standard' for the measurement of adherence and the use of various measures have been reported in the literature (37). One form of measurement involves asking patients to self-report adherence behaviour. Although self-report is a subjective measure that can present with respondent bias and overestimation of adherence (40), it has been considered the method of choice for clinical use as it is cheap, relatively unobtrusive, has the potential to be implemented in clinical workflow and able to distinguish between intentional and unintentional nonadherence (42, 44). Self-reported measures such as questionnaires, the Morisky scale (45), TABS adherence scale (41), medication diaries and qualitative interviews have been widely used in the general population. Self-reported measures can be documented at a single timepoint or may require recall of information. Measures that are associated with less potential respondent bias include manual or electronic pill counting. Electronic monitoring is considered to be one of the most accurate methods of measuring adherence (46). The Medication Event Monitoring System (MEMS®) is an example of electronic monitoring of adherence that records the date and time when the package is opened to remove medication. Although they have the advantage of being a dynamic measure, they do not prove ingestion (46). Nevertheless, several studies have demonstrated moderate to strong associations between electronically monitored adherence and improvement in clinical biomarkers, making them a commonly used intervention in the improvement of patient adherence in the U.S (44). However, their expense precludes their widespread use (37). Moreover, a review of medication adherence reported that patients commonly improve their medication adherence in the 5 days before and after an appointment with the health care professional, compared with 30 days after, a phenomenon termed white-coat adherence (47).

The rate of pharmacy prescription refills via pharmacy databases is another common measure. This measure can be used to check when the prescription is initially filled, refilled over time, and prematurely discontinued, but also does not ensure ingestion of the medication (37). Adherence measured in this way is moderately correlated with adherence measured by electronic monitoring (44). Objective clinical measurements, such as drug concentration in the blood or the measurement of clinical parameters (e.g. BP), can also be used as a 'surrogate' to measure adherence (47,48); however, their utility during pregnancy is limited because many physiological factors impact on drug levels and the progression of hypertension during pregnancy (49). Moreover, the duration of

medication taking during hypertensive disorders of pregnancy is often limited to a short period from the time of diagnosis until delivery (6) limiting the concentration of the drug in the blood available for testing.

Furthermore, adherence measures that rely heavily on recall can often under or overestimate adherence. Feldman et al. (50) studied the determinants of recall and recall bias in studying drug and chemical exposure during pregnancy. The results suggest that recall of chronically used medications during pregnancy is better than that for acutely used ones (50). In addition, the authors did not find any discrepancies in recall between women who delivered babies with major anomalies compared to normal outcomes. This result was different to the finding in a retrospective study of a group of pregnant women who took itraconazole during the first trimester, resulting in congenital malformations (51). Bar-Oz et al. reported that the women who had taken itraconazole during pregnancy reported less use of the medication compared to prospectively obtained drug utilisation data (13.0 vs. 3.2%, $p = 0.006$) (51). These results are supported by the observation that 'differential recall is a serious threat when data are collected after the outcome of the disease is known by the respondents' (50-52). As suggested by these studies (48, 51, 53), a combination of quantitative and qualitative adherence measures (i.e. a triangulation approach) would be the most useful approach to properly measure adherence to medications.

1.7 Statement of the problem

Considering that hypertensive disorders complicate approximately 10% of all pregnancies in Australia (6) and can adversely affect both the mother and the baby during the pregnancy and beyond, a multidisciplinary management approach which incorporates the perspectives of the women should be adopted to optimise care and outcomes.

Despite extensive clinical research into optimising the management of HDP and potentially reducing the adverse impact onto to the mother and baby, no previous research has investigated how effective the management is, from both a system and patient perspective. Similarly, the patient experience has not been previously explored in depth or taken into regard when attempting to optimise the management of women with HDP.

The efficacy of any treatment is maximised by optimal medication adherence. Conversely, nonadherence to medication can contribute significantly to treatment failure and unnecessary over-prescribing. In a study of 819 pregnant women who were surveyed at their 36 week antenatal visit at a tertiary hospital in Melbourne, cardiovascular medicines were among those associated with self-reported nonadherence (54). Adherence to antihypertensive medication in the Australian general adult population is also known to be a problem (55, 56). A systematic review of 53 qualitative studies on

patients' understanding and experiences of hypertension and medication showed that non-adherence to antihypertensive medication resulted from lack of understanding of the causes and effects of hypertension (57). Poor medication tolerability, complex dosage schedules and poor health literacy are just a few of the factors associated with adherence to antihypertensive medications in the general population. It is not known whether these factors also impact adherence to antihypertensive medication during pregnancy. Health beliefs about the illness is another factor that can impact on adherence (58). During pregnancy, the fear of potential teratogenicity is often over-estimated and can also impact on adherence (59).

The beliefs, experiences, attitudes and behaviours of women who are prescribed antihypertensive medications to help control their BP during pregnancy have not been previously explored in depth.

1.8 Overview of the research

1.8.1 Aims and objectives

This research aimed to provide an understanding of management of hypertensive disorders of pregnancy and medication use during pregnancy.

The specific objectives were to:

i. provide an understanding of the management of hypertension in the Australian context. This involved investigating compliance to Australian guidelines, specifically:

   a. thresholds for initiation of antihypertensive therapy;
   b. appropriateness of medication regimens; and
   c. use of aspirin in women with known risk factors for development of pre-eclampsia.

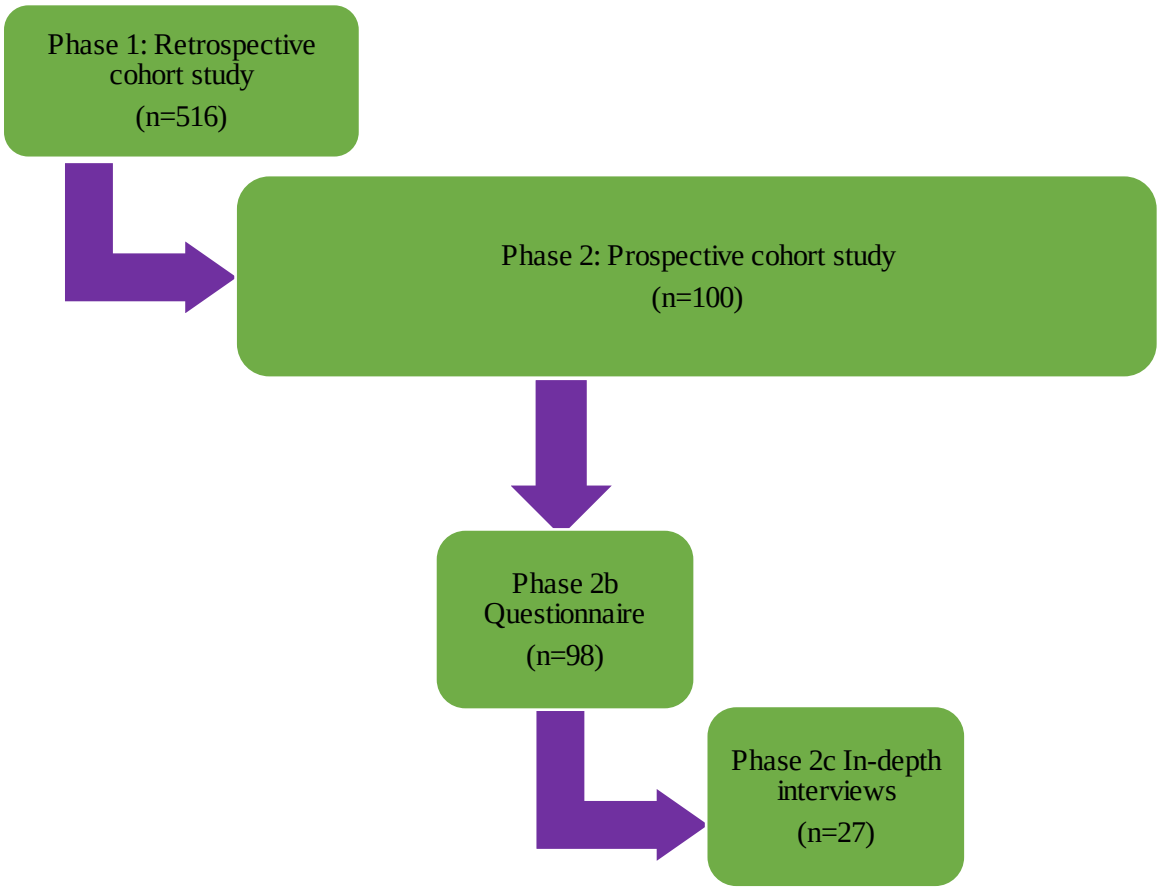
ii. estimate the rate of non-adherence to antihypertensives during pregnancy;

iii. understand the women's perspectives on adherence to medication and management of their hypertensive disorder of pregnancy; and

iv. contextualise the women's perspectives via documentation of management and outcomes.

1.8.2 Project scope

The research was conducted in two main phases, with the second phase comprising three sub-phases, each with specific objectives, as illustrated in **Figure 1.1.** The details of each phase are further discussed below and in **Chapters 3 to 7**.



Phase 1 Retrospective cohort study

To provide an understanding of the management of hypertension in the Australian context.

Phase 2 Prospective cohort study

To contextualise the women's perspectives via documentation of management and outcomes.

Phase 2b Prospective cohort study - questionnaire

To estimate the rate of non-adherence to antihypertensives during pregnancy.

Phase 2c Prospective cohort study - in-depth interviews

To understand the women's perspectives on adherence to medication and management of their hypertensive disorder of pregnancy.

Figure 1.1 Project Scope

1.8.3 Overview of thesis structure

This thesis by publication is presented in 8 chapters. **Chapter 1** provides a general overview of the thesis and includes the research aims and objectives. **Chapter 2** provides a detailed background to the research and a review of the current literature around the management of hypertensive disorders of pregnancy; adverse outcomes of HDP on mother and baby; safety of antihypertensive medication during pregnancy and use of antihypertensive medications during pregnancy. The subsequent chapters (3, 4, 5, 6 and 7) present the two phases of the research in detail. **Chapter 3** presents the findings of the retrospective cohort study, including a manuscript published in the Australian and New Zealand Journal of Obstetrics and Gynaecology. **Chapter 4** presents the findings of a questionnaire, which included an adherence scale, from the prospective cohort. This chapter includes a manuscript that is published in Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. **Chapter 5** presents the qualitative findings relating to the use and adherence of antihypertensive medication during pregnancy. This chapter includes a manuscript that is published in SAGE Open Medicine. **Chapter 6** presents the qualitative findings relating to the women's perspectives of the management of HDP. This chapter includes the manuscript that is published in BMC Health Services Research. **Chapter 7** presents the findings of the prospective cohort regarding the hospital's management of HDP. This chapter includes a manuscript has been revised and resubmitted to Obstetric Medicine. **Chapter 8** summarises and discusses the overall findings of the research. This chapter also presents recommendations to practitioners and researchers, discusses strengths and limitations of the studies, and proposes future research directions and implications for clinical practice.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

As outlined in **Chapter 1**, the research in this thesis focuses on understanding the management of hypertensive disorders of pregnancy (HDP) and medication use. The purpose of this chapter is to provide a general overview to facilitate the understanding of the nature of HDP and their management, and to summarise the literature from previous studies regarding optimisation of management. The use of medication in general by pregnant women is also examined. The review begins with a snapshot of the epidemiology of HDP globally and in Australia (**Section 2.2**). In **Section 2.3**, the definition and classification of HDP are presented, with a comparison across national and international guidelines, leading to **Section 2.4**, examining various aspects of the clinical management of HDP across different countries, with an illustration of how management has evolved over the last decade. Adverse outcomes of HDP are discussed in **Section 2.5**, including those of pregnancy and delivery, perinatal complications and long-term adverse outcomes for both the mother and the offspring. **Section 2.6** provides a review of the safety of antihypertensive medications during pregnancy and **Section 2.7** outlines the use of antihypertensives during pregnancy.

2.2 Epidemiology of hypertensive disorders of pregnancy globally and in Australia

HDP complicate approximately 10% of all pregnancies in Australia (6) a rate that is similar to high income countries internationally (60) . Combined, they are the second largest cause of maternal death, after haemorrhage, in the developed world (7). In a report from the Australian Institute of Health and Welfare (AIHW) about maternal deaths, HDP was the third largest cause of direct maternal death in Australia, after thromboembolism and haemorrhage (61). Thus, there is substantial interest in understanding this complication in the obstetric literature.

Wang et al. conducted a population-based study focusing on epidemiological profiles of HDP from global data to determine the trends of HDP from 1990 to 2019 and its global incidence (60). The authors reported a decrease in death and incidence rates in most countries and regions of world, except for those with low sociodemographic human development indexes (60). Several other epidemiological studies have determined the prevalence of HDP globally, in various countries/regions of the world (62-64). Slight variation in the estimates of HDP prevalence between regions is evident when reviewing these studies. Gemechu et al. performed a systematic review and meta-analysis of

epidemiological studies relating to the prevalence of HDP in Sub-Saharan Africa (62). An overall prevalence of 8% was determined from 70 studies (62). Li et al. conducted a systematic review and meta-analysis examining the prevalence of HDP in China (63). A combined prevalence of 7.3% from 92 studies was determined (63). Olie et al. performed a prospective cohort study using the French National Health Insurance System to determine the prevalence of HDP in France and found a 7.4% prevalence (64).

Roberts et al. were the first to describe the prevalence of HDP in Australia and link them to maternal and infant outcomes in 2005 (65). The authors reported that of the 24,517 studied women, HDP affected 9.8% of pregnancies with the breakdown being chronic hypertension 0.6%, pre-eclampsia 4.2%, pre-eclampsia superimposed on chronic hypertension 0.3% and gestational hypertension 4.3% (65) (These HDP subtypes are discussed further in S 2.3.). As this study was a cross-sectional using linked population databases, information about clinical management was not available for discussion. Thornton et al. studied the prevalence of pre-eclampsia and eclampsia in New South Wales, Australia between the years 2000 and 2008 via a population-based surveillance system named the NSW Midwives Data Collection (66). The authors reported an overall rate of pre-eclampsia of 3.3% of singleton births (22,827 cases from 691,738 births) (66). HDP prevalence estimates may also differ when different definitions of HDP are used. These definitions are discussed further in S 2.3. There has been a paucity of population-based studies investigating the prevalence of HDP in Australia after Roberts et al. (65) and Thornton et al. (66). Moreover, there were no similar population-based systems in Victoria at the time of the initiation of this PhD project.

2.3 Definition and classification of hypertensive disorders of pregnancy

2.3.1 Definition of hypertensive disorders of pregnancy

An insight into the changes in blood pressure (BP) of normotensive pregnant women is crucial to the understanding of the diagnosis and classification of HDP. BP usually decreases in early pregnancy and reaches its lowest point during the early part of the second trimester when the diastolic BP is, on average, 15mmHg lower than the pre-pregnancy value (6, 12). BP then rises during the third trimester and reaches pre-pregnancy levels by term (6, 12). A recent systematic review and meta-analysis of BP and heart rate in normal pregnancies reported that, although diastolic BP is the lowest mid-pregnancy, it does not decrease as substantially as previously thought (67). The substantial decrease of BP, however, currently remains the stance of international and national guidelines (6, 68).

In Australia, the clinical guidelines of the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) (6) guide the definition, classification and management of HDP. Internationally, there are four main recognised clinical guidelines for HDP; namely from the International Society for

the Study of Hypertension during Pregnancy (ISSHP) (68), the National Institute for Health and Care Excellence (NICE) (69) from the UK, the American College of Obstetricians and Gynecologists (ACOG) from the USA (70,71) and the Society of Obstetricians and Gynaecologists of Canada (SOGC) (72). There are similarities and differences among the various guidelines when it comes to the definition of HDP (summarised in Table 2.1). There have been some changes to the definition of HDP over the last decade, which are also detailed in Table 2.1. The levels chosen are consistent with the diagnosis of mild hypertension in the general adult Australian (73) and British (74) populations, but not the Canadian (75) and American (76) populations as shown in Table 2.1. Although lowering of the BP threshold for diagnosis of hypertension may increase the prevalence of HDP and potentially identify more women at risk of pre-eclampsia, further research is needed before changing this level, as a lower target BP has a risk of poor placental perfusion (6, 77).

Table 2.1: Definitions of HDP: comparison of different guidelines and changes over time

Guideline	**Definition of hypertension**	**Definition of mild hypertension in current national guidelines for general adult population**	**Definition of severe hypertension**
SOMANZ 2008[78]	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg		SBP ≥ 170 mmHg and/or DBP ≥ 110 mmHg
2014[6]	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg[66]	SBP ≥ 170 mmHg and/or DBP ≥ 110 mmHg
ISSHP 2001[79]	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg		SBP ≥ 170 mmHg and/or DBP ≥ 110 mmHg
2018[68]	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg		SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg
NICE 2010 [80]	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg		SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg
2019[69]	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg[67]	SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg

Guideline	Definition of hypertension	Definition of mild hypertension in current national guidelines for general adult population	Definition of severe hypertension
SOGC 2008[81]	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg		SBP ≥ 160 mmHg and/or DBP ≥ 105 mmHg
2014[72]	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg	SBP>135 mmHg or DBP >85 mmHg[68]	SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg
ACOG 2000[82]	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg		SBP ≥ 160 mmHg and/or DBP ≥ 105 mmHg
2019[70,71,83]	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg	SBP130–139 mmHg DBP 80–89 mmHg[69]	SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg

SBP: systolic blood pressure
DBP: diastolic blood pressure

Although the current SOMANZ guideline (6) still defines severe hypertension as SBP greater than or equal to 170 mmHg and/or DBP greater than or equal to 110 mmHg, they do recommend antihypertensive treatment for all pregnant women with BP greater than or equal to 160 mmHg SBP or 110 mmHg DBP. They also emphasise that severe hypertension requires urgent treatment and represents a level of BP above which the risk of maternal morbidity and mortality is increased (6).

2.3.2 Classification of hypertensive disorders of pregnancy

As mentioned in Chapter 1, there are two broad categories of HDP: those that are chronic and existed pre-pregnancy and those that are pregnancy-induced, known as gestational. The classification of the HDP reflects the pathophysiology of the condition as well as the risks it poses for the mother and the fetus (6). The standard classification of these disorders was first done by Davey and MacGillivray in 1988 (84). The current classification of HDP is generally agreed upon amongst national and international clinical guidelines. The only classification where there are some differences are in the diagnosis of pre-eclampsia (this is explained later in this sub-section, pp 18-25). For the research described in this thesis, the classifications, definitions and sub-types of the SOMANZ clinical guidelines (6) were used in the inclusion criteria and analysis of the study cases. The classification endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) in their

revised statement in 2014 (85) is the same categorisation adopted by SOMANZ in the Australian clinical setting (6).

The classification of the sub-types of HDP is as follows:

- Chronic hypertension
  - Essential
  - Secondary
  - White coat
- Gestational hypertension
  - Gestational hypertension
- Pre-eclampsia
  - Pre-eclampsia
  - Pre-eclampsia superimposed on chronic hypertension
  - Haemolysis, elevated liver enzymes and low platelet syndrome (HELLP)
  - Eclampsia

2.3.2.1 Chronic Hypertension

Essential chronic hypertension is defined as (6):

- the presence of hypertension before 20 weeks of gestation
- without a known cause
- without the clinical features of pre-eclampsia.

Secondary chronic hypertension is defined as (6):

- the presence of hypertension before 20 weeks of gestation
- with a known cause
- without the clinical features of pre-eclampsia.

Chronic hypertension is thus a hypertensive disorder that can exist pre-pregnancy. In the past, it was known that women tended to have lower BP than men and progress to hypertension later in life, often bypassing the child bearing years (86). More recently, the incidence of metabolic syndrome and obesity in women of childbearing age in the developed world has been steadily increasing, thus increasing the prevalence of essential hypertension (6, 87). Moreover, the trend of childbearing at an older age also contributes to the increased incidence of chronic hypertension during pregnancy (6, 87). A study by Ananth et al. (88) investigated the change in prevalence of chronic hypertension in pregnancy from 1970 to 2010 via a population-based cross-sectional analysis of 151 million women

with delivery-related hospitalisations in the USA in that time period. The rate of chronic hypertension was found to have increased sharply with advancing age of pregnancy from 0.11% in 1970 to 1.52% in 2010 (rate ratio, 13.41; 95% CI, 13.22-13.61) (88). Although similar studies have not been conducted in Australia, it can be assumed that this sharp increase would also be seen in a similar developed country. It is estimated that chronic hypertension accounts for about 1-2% of the overall cases of HDP (6, 87).

Decrease in BP in early pregnancy, as described in the normotensive mother, also occurs in women with chronic hypertension (89, 90). This can result in the pregnant mother mistakenly misdiagnosed with gestational hypertension when the BP begins to increase again after 20 weeks gestation (89, 90). It is thus important to monitor the BP of pregnant women from the beginning of pregnancy and, if possible, BP readings should be obtained before pregnancy.

Secondary hypertension accounts for approximately 11.2% of total chronic hypertension in pregnancy cases (91). The most common cause of secondary hypertension is chronic kidney disorder (91). Other causes include aldosteronism, renovascular hypertension, Cushing's syndrome, pheochromocytoma, thyroid disease (which occurs in 4.1 % of pregnant women with chronic hypertension), systemic lupus erythematosus, scleroderma, connective tissue diseases, maternal coarctation of the aorta and congenital heart disease (91, 92). Pregnancies affected by a secondary cause of hypertension can pose unique maternal and fetal risks and even maternal deaths (92). It is therefore important for these disorders to be diagnosed pre-conception to allow early optimal management of the disease (91).

White coat hypertension (WCH) during pregnancy is classified as chronic hypertension and is defined by the ISSHP (68) as an elevated clinic BP (≥140/90 mmHg) but a normal BP measured at home or work and is similar to WCH outside pregnancy (93). An estimated 1 in 4 patients in the general adult population have WCH, however, the incidence in pregnancy has been inconsistently reported in the literature (68), ranging from 4% (87, 88) to 30% (96, 97). The ISSHP considers ambulatory BP monitoring or self-monitoring of BP (SMBP) mandatory in pregnant women with WCH (68). A recent meta-analysis and systematic review of maternal and perinatal outcomes of white coat hypertension during pregnancy found that WCH is associated with a worse perinatal and maternal outcomes than for those who were normotensive, but better outcomes than for those with gestational hypertension and chronic hypertension (93). The authors therefore concluded that a diagnosis of WCH should be ascertained in pregnant women presenting with hypertension and should not be dismissed as insignificant (93). Similarly, the ISSHP notes that WCH is not a benign condition and carries a higher risk of pre-eclampsia (68). Moreover, when the diagnosis is confirmed, these women require monitoring for developing pre-eclampsia, small-for-gestational-age and pre-term birth just like other women with HDP (68).

ISSHP alone has an added classification known as masked hypertension. This is defined as BP that is normal at a clinic visit but elevated at other times, most typically diagnosed by 24-hour ambulatory BP monitoring (68).

2.3.2.2 Gestational Hypertension

Gestational hypertension is defined as (6):

- the new onset of hypertension after 20 weeks gestation
- without maternal or fetal features of pre-eclampsia
- followed by the return of BP to normal within three months post-partum.

Gestational hypertension complicates more hypertensive pregnancies than chronic hypertension and pre-eclampsia. Current estimates of the prevalence of gestational hypertension are not clear and are often grouped with pre-eclampsia. Together, these disorders represent the remaining 7% of the 10% of pregnant women affected by hypertension (77, 98).

The earlier the stage of gestation at presentation, or the more severe the hypertension, the higher the risk of developing pre-eclampsia (77, 99). Saudan et al. also found that approximately 15-25% of pregnant women with gestational hypertension progressed to pre-eclampsia. This was found to be more likely when the hypertension appeared before 34 weeks gestation and if there had been a prior miscarriage (99).

2.3.2.3 Pre-eclampsia

Pre-eclampsia alone is estimated to account for at least 42,000 maternal deaths annually worldwide (100). The current definition of pre-eclampsia in the aforementioned guidelines is 'a multi-system disorder of pregnancy characterised by gestational hypertension and the involvement of one or more organs and/or the fetus' (6, 78). Recent advances in pre-eclampsia research, particularly the involvement of the placenta and placental factors has led some experts in the field to modify this definition to: 'Pre-eclampsia is a multisystem pregnancy disorder characterised by variable degrees of placental malperfusion, with release of soluble factors into the circulation' (101).

Pre-eclampsia (previously referred to as toxaemia of pregnancy) has been documented for almost 200 years whilst eclampsia, which involves seizures and potential coma, has reportedly been documented for 2,400 years (102). Despite this, the pathophysiology remains poorly understood, limiting therapeutic interventions. In recent years, however, there have been some advances in research into

the pathophysiology, potential therapies and screening tools (these are also discussed later in this section, pp 22-23 and S 2.4).

The epidemiological studies mentioned in S 2.2 reported the combined prevalence of HDP, as this was relevant to the study population of this thesis. This type of reporting, however, is not commonplace in the HDP literature, as noted in a review by Umesawa et al. (103). Instead, most epidemiological studies focus on one subtype of HDP or another, the most common being pre-eclampsia. Auger et al. conducted a large population-based longitudinal study to investigate the incidence of pre-eclampsia over 24 years in Canada (104). They reported an increase in the incidence of pre-eclampsia from 2.64% in 1989 to 5.06% in 2012 with no increase in adverse maternal outcomes over time (104). The authors related this increase in incidence to the global rise of obesity and other metabolic disorders (104). Another explanation for this increase may be the significant broadening of the definition of pre-eclampsia from 1989 to 2012 (105).

Following the classification of HDP by Davey and MacGillivray, the presence of new onset of proteinuria was mandatory for the diagnosis of pre-eclampsia (84). Although a new onset of proteinuria during pregnancy is frequently associated with the diagnosis of pre-eclampsia, it is no longer mandatory for the diagnosis (6, 78). As such, the diagnostic criteria for pre-eclampsia have evolved from the traditional definition of new onset hypertension and proteinuria to a broader definition of hypertension with evidence complex multi-organ system involvement caused by the disease (101, 106). This is in agreement with the ISSHP guideline that was updated just before the SOMANZ 2014 guideline was finalised (85). In light of this, the SOMANZ 2014 guidelines have devised more detailed diagnostic criteria for pre-eclampsia, as indicated in Table 2.2. The diagnosis of pre-eclampsia necessitates the presence of gestational hypertension with at least one other feature (Table 2.2).

Table 2.2: Pre-eclampsia features necessary for diagnosis as per international guidelines

Guideline	Mandatory GH	Renal	Haemato-logical	Liver	Neuro logical	Pulmonary oedema	Utero-placental dysfunction	Angiogenic markers
SOMANZ 2014[6]	✓	✓	✓	✓	✓	✓	✓ (FGR only)	×
ISSHP 2018[68]	✓	✓	✓	✓	✓	✓	✓ (detailed)	✓
NICE 2019[69]	✓	✓	✓	✓	✓	✓	✓	×
SGOC 2014[72]	✓	✓	✓	✓	✓	✓	✓	×

Guideline	Mandatory GH	Renal	Haemato-logical	Liver	Neuro logical	Pulmonary oedema	Utero-placental dysfunction	Angiogenic markers
ACOG 2019[70]	✓	✓	✓	✓	✓	✓	✓	×

GH = Gestational hypertension (new onset of hypertension after 20 weeks of gestation)
FGR = Fetal growth restriction

It is important to note that only SOMANZ 2014 considers FGR alone as defining pre-eclampsia in the presence of hypertension (6). ISSHP 2018 comments that controversy remains as to whether FGR in the context of new-onset gestational hypertension, without any other maternal feature of pre-eclampsia, should define pre-eclampsia (68). Despite this, the ISSHP 2018 authors' view was that this should apply given that pre-eclampsia is, most commonly, of itself a primary placental disorder (68). Furthermore, to address this controversy, the ISSHP, NICE and Canadian guidelines detailed other uteroplacental dysfunctions including: oligohydramnios, absent or reversed end-diastolic flow by Doppler velocimetry, placental abruption with evidence of maternal or fetal compromise, reverse ductus venosus A wave, and stillbirth (68, 69, 72).

The ISSHP 2018 guideline provides the most detailed and broad definition for pre-eclampsia, which includes all of the maternal factors defined by SOMANZ with the addition of a more detailed definition of fetal growth restriction. This is defined according to the gestation scan which takes place from 35 to 36 weeks and 6 days as either estimated fetal weight 95th percentile, umbilical artery pulsatility index >95th percentile, or middle cerebral artery pulsatility index 95th percentile (68). The ISSHP is the only guideline that gives an angiogenic imbalance definition, defined as placental growth factor <5th percentile soluble fms-like tyrosine kinase-1- to serum placental growth factor >95th percentile (68). There remains, however, a controversy with regard to the implementation of broader definitions and the most appropriate definition of end-organ dysfunction (106). Reddy et al. performed a retrospective study of singleton pregnancies at a major hospital in Melbourne between January 1, 2016 and July 31, 2018 (106). All cases of gestational hypertension and pre-eclampsia were reclassified according to the ISSHP 2001, American College of Obstetricians and Gynecologists 2018, and the ISSHP 2018 criteria. GH incidence was found to be the same amongst all three guidelines, as indicated by the unchanged definition as per Table 2.1. Of 22,094 pregnancies, 751 (3.4%) women had PE as defined by any of the three criteria. Compared with ISSHP 2001, the ACOG 2018 criteria identified an extra 42 women (n=654 vs n=696, 6.4% relative increase) with pre-eclampsia, and ISSHP 2018 identified an extra 97 women (n=654 vs n=751, 14.8% relative increase) (106). The authors also found that women who exclusively fulfilled the ISSHP 2018 criteria had milder pre-eclampsia. This led them to conclude that although implementation of broader definitions of pre-eclampsia will result in an increased incidence of disease diagnosis, it remains uncertain

whether this will translate to improved clinical outcomes (106). Moreover, the use of a less broad definition of pre-eclampsia may result in an oversight of cases, which may in turn compromise the care of the pregnant women and her fetus.

The pre-eclampsia definition that was used for the research in this thesis was that of the SOMANZ 2008 guidelines. These guidelines dictated that pre-eclampsia is diagnosed when a new onset of hypertension arises after 20 weeks gestation and is accompanied by one or more of the following (78):

Renal involvement

Significant proteinuria: a spot urine protein/creatinine ratio ≥ 30mg/mmol

Serum or plasma creatinine > 90 μmol/L

Oliguria <80mL/4 hr

Haematological involvement

Thrombocytopenia <100,000 /μL

Haemolysis: schistocytes or red cell fragments on blood film, raised bilirubin, raised lactate dehydrogenase >600mIU/L, decreased haptoglobin

Disseminated intravascular coagulation

Liver involvement

Raised serum transaminases: alanine aminotransferase or aspartate aminotransferase >40 IU/L) (68)

Severe epigastric and/or right upper quadrant pain

Neurological involvement

Convulsions (eclampsia)

Hypereflexia with sustained clonus

Persistent, new headache

Persistent visual disturbances (photopsia, scotomata, cortical blindness, posterior reversible encephalopathy syndrome, retinal vasospasm)

Stroke

Pulmonary oedema

Accumulation of fluid in the pulmonary interstitial spaces and alveoli

Fetal growth restriction (FGR) < 10^{th} centile

Pre-eclampsia is generally recognised as a complication of first pregnancy (107) but can also occur in subsequent pregnancies (102, 108). As described above, pre-eclampsia can be diagnosed in many different ways, either after the pregnant woman has had severe epigastric pain, significant proteinuria, persistent new headache or seizure, to name a few. The symptoms are often sudden with little

introduction and although treatment for the progression of this disease has been highly sought, it has not yet been found (101).

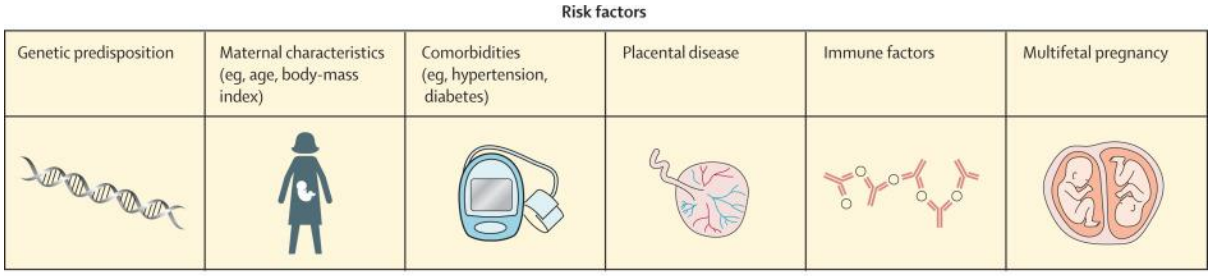
The risk for the development of pre-eclampsia in pregnant women with chronic hypertension is significant, estimated at around 25% (109, 110). Moreover, the rate of pre-eclampsia superimposed on chronic hypertension in pregnant women with severe hypertension is close to 50% (111).

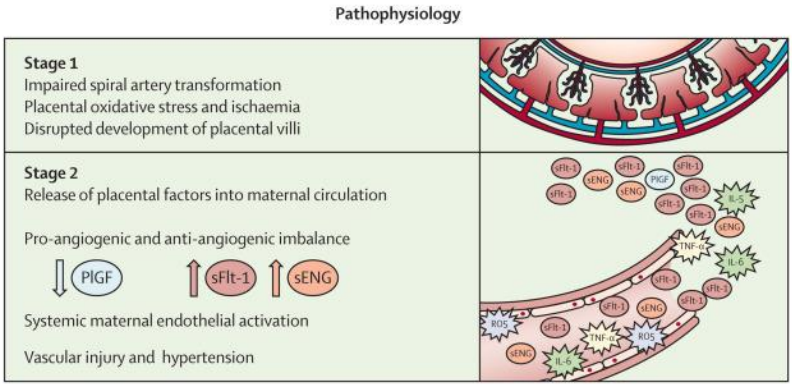
Pre-eclampsia is regarded as serious if severe hypertension is associated with proteinuria or if hypertension is combined with severe proteinuria of ≥ 5g per day (112). The maternal complications of severe pre-eclampsia include placental abruption (1-4%), acute renal failure (1-5%), eclampsia (<1%), disseminated coagulopathy (10-20%), liver failure or haemorrhage (<1%), stroke (rare) and death (rare) (108). Neonatal complications include premature delivery (15-67%), fetal growth restriction (10-25%), hypoxia leading to neurological injury (<1%) and perinatal death (1-2%) (108).

Known risk factors for pre-eclampsia include (101, 102, 108, 113):

- Chronic hypertension
- Antiphospholipid antibody syndrome
- Systemic lupus erythematosus
- Pre-gestational diabetes
- Chronic renal disease
- Multifetal pregnancy
- Pre-pregnancy BMI >30
- Previous stillbirth
- Nulliparity
- Maternal age >40 years
- Long inter-pregnancy interval (>5 years)
- Reduced school education
- Previous pre-eclampsia
- Assisted reproduction
- Previous intrauterine growth restriction (IUGR)
- Previous placental abruption

In recent years, understanding of the pathogenesis of pre-eclampsia has furthered research that is getting closer to potential treatments for pre-eclampsia. Figure 2.1 outlines the current understanding of the pathophysiology of pre-eclampsia as described by Chappell et al. who are experts in the field of pre-eclampsia and recently published an expert review (101).





Multiorgan dysfunction

		Symptoms	Signs	Investigations	Complications
	Neurological	Headache and visual disturbances	Brisk reflexes and clonus	..	Eclampsia, posterior reversible encephalopathy syndrome, and intracranial haemorrhage
	Renal	..	..	Proteinuria and raised serum creatinine	Acute kidney injury
	Hepatological	Epigastric pain	Right upper quadrant tenderness	Elevated serum liver enzymes	Hepatic haematoma or rupture
	Haematological	..	Dark brown urine and petechiae	Low platelets, abnormal clotting tests, and haemolysis	Coagulopathy
	Uteroplacental and fetal	Vaginal bleeding and reduced fetal movements	Hard uterus and reduced fundal height	Fetal growth restriction	Placental abruption and intrauterine fetal death
	Cardiorespiratory	Breathlessness, chest pain, and confusion	Tachypnoea	Decreased oxygen saturation and diastolic dysfunction	Pulmonary oedema

Figure 2.1 Pathophysiology of pre-eclampsia (101)

Reprinted from Pre-eclampsia, Chappell L, Cluver C, Kingdom J, Tong S The Lancet 2021 Jul 24;398(10297):341-354. doi: 10.1016/S0140-6736(20)32335-7, Copyright (2021), with permission from Elsevier.

In summary, the current understanding is that pre-eclampsia is a disorder of pregnancy characterised by variable degrees of placental malperfusion, with release of soluble factors such as proinflammatory cytokines, exosomes (114) and extracellular vesicles (115); and anti-angiogenic molecules such as soluble fms-like tyrosine kinase-1 (sFlt1), placental growth factor (PlGF) and soluble endoglin (116) into the circulation. These placental factors cause maternal vascular endothelial injury, leading to hypertension and multi-organ injury. The placental disease can also cause fetal growth restriction and

perinatal death (101). Furthermore, several reports have shown that the angiogenic and antiangiogenic factors that are involved in the pathogenesis have possible relevance in the diagnosis and prognosis of pre-eclampsia (117). The main placental factors of interest are FMS-like tyrosine kinase receptor-1 (sFlt1), an antagonist of vascular endothelial growth factor, and placental growth factor (PlGF). The test is based on a ratio of these factors whereby an increased serum level of sFlt-1 and decreased level of PlGF result in an increased sFlt1/PlGF ratio. This measure can detect the progression to not only pre-eclampsia, but also to IUGR and stillbirth. This can be detected using a blood test in the second half of pregnancy (117). Disturbances in these angiogenic factors have been reported to be detectable prior to the onset of clinical symptoms of pre-eclampsia or IUGR, thereby allowing distinction of women with healthy pregnancies from those at high risk for primarily developing pre-eclampsia (117).

Although this pathophysiology is generally agreed upon, there is currently a debate around the aetiology of pre-eclampsia in the obstetric literature. Murthi and Brennecke (118) report that, when the placenta releases the aforementioned factors, this causes injury to other organs and is thus the villain. On the other hand, Thilaganathan et al. argue that the placenta is a victim of maternal cardiovascular dysfunction, citing abundant evidence from peripheral waveform analysis (uterine, radial and ophthalmic artery Doppler), maternal echocardiography, and angiogenic marker studies that maternal cardiovascular dysfunction precedes the development of pre-eclampsia by several weeks to months (119, 120). Further research is required to prove or disprove these theories. If, however, the theory that maternal cardiovascular dysfunction is the source of pre-eclampsia aetiology, then routine cardiovascular screening of women at high risk of developing pre-eclampsia may assist in identifying the disease early and, if the cardiovascular dysfunction is modifiable, it may also alter the outcome of the disease.

HELLP is a serious manifestation of pre-eclampsia and is not regarded as a separate disease (6, 68). Lisonkova et al. performed a retrospective population-based cohort study investigating the incidence of HELLP syndrome in Canada. ICD-10-CA diagnostic code from delivery hospitalisation data was used for mothers with a singleton hospital live birth or stillbirth at ≥24 weeks' gestation (n=1,078 323) 2012/2013–2015/2016 (121). They reported an incidence of 2.5 per 1,000 singleton deliveries and that HELLP syndrome was associated with a higher maternal death rate, and substantially higher severe maternal and neonatal morbidity and perinatal mortality compared to any other subtype of HDP (121).

Eclampsia is a rare but serious manifestation of HDP where seizures occur during a woman's pregnancy or shortly after giving birth (6). Classically, headache, visual disturbance or an altered level of consciousness are considered the symptoms of imminent eclampsia; however, there are no reliable clinical markers that predict eclampsia and, conversely, the presence of neurological symptoms and/or

signs is rarely associated with seizures (6). Seizures may occur antenatally, intra-partum or postnatally, usually within 24 hours of delivery but occasionally later (6). Fishel and Sibai report the incidence of eclampsia as 1.6 to 10 per 10,000 deliveries in developed countries and 50 to 151 per 10,000 deliveries in developing countries (122). They relate this discrepancy to differences in antenatal care and timing of delivery between developed and developing countries (122). Pollock et al. conducted a two-year population-based descriptive study investigating the incidence of eclampsia in Australia and New Zealand in 2010-2011 (123). One hundred and thirty-six women were found to have had eclampsia, 111 (83%) in Australia and the remaining 25 (17%) in New Zealand. The estimated incidence of eclampsia was 2.2 (95% confidence interval (CI) 1.9-2.7) per 10,000 women giving birth, with an over-representation amongst Aboriginal and Torres Strait Islander people in Australia (123).

2.4 Management of hypertensive disorders of pregnancy

The main facets of management of HDP are BP control, prevention and management of pre-eclampsia (and thus eclampsia), fetal monitoring and the timing of delivery (1). The management of HDP varies according to the classification of the hypertensive disorder as well as the severity of the disease. Unlike gestational diabetes, which is often managed by the obstetrician and/or an endocrinologist (124), HDP is usually managed by the obstetrician without cardiologist input. This can potentially result in a wide variation of treatment modalities, often based on the clinical experience of individual obstetricians with an interest in the treatment of HDP, the involvement or lack thereof of an obstetric physician with an interest in the treatment of HDP, as well as evidence from the medical literature. There are, however, five main internationally recognised management guidelines often referred to in the literature, as mentioned in S 2.3.

2.4.1 Blood pressure control in pregnancy

Monitoring of BP is the cornerstone of BP control during pregnancy. This monitoring can occur at the hospital and also at home via increasing encouragement of SMBP. The use of antihypertensive medication is also important in many cases of HDP. As mentioned in S 2.3, hypertension can be considered as either severe or mild-moderate. The most commonly used antihypertensive medications during pregnancy are: labetalol, methyldopa and nifedipine (6). IV hydralazine and IV labetalol are reserved for severe hypertension (6).

2.4.1.1 Blood pressure monitoring during pregnancy

In Australia, BP is measured and recorded for every pregnant woman at each antenatal visit regardless of whether a diagnosis of HDP has been made. This regular measurement of BP during pregnancy is essential for the diagnosis and management of hypertension. Australian hospitals with maternity services also have pregnancy day assessment units, where the BP is checked every half an hour over a 4-hour period to assess worsening BP or to confirm diagnosis of gestational hypertension and avoid potentially unnecessary hospitalisation (6, 125). These units are staffed by midwives with an obstetric registrar on call if a medical intervention is required (126). The diagnosis of gestational hypertension is often confirmed or negated in this scenario. It is also where many women are initiated on antihypertensive treatment for HDP.

The incremental increase in plasma volume during a normal pregnancy is well documented (127); thus, the recommended method of measuring BP in pregnant women is quite specific. The SOMANZ guidelines recommended that (6, 78):

- Pregnant woman should be seated comfortably with her legs resting on a flat surface
- Measurement of BP from both arms should be undertaken at the initial antenatal visit to exclude any rare vascular abnormalities such as aortic coarctation, subclavian stenosis and aortic dissection. BP should be measured at subsequent visits using the right arm if there is little difference in BP between the two limbs (a variation of up to 10mmHg is acceptable)
- Correct cuff size is necessary for the accurate measurement of BP and to minimise the over-diagnosis of hypertension

The use of SMBP during pregnancy was first described in 1989 by Margulies et al. (128). They documented that the variation in the pattern of BP between the waking and sleeping values in 11 normotensive women in the third trimester of pregnancy was similar to that of the non-pregnant population. This prompted further research into the use of SMBP for the detection and management of hypertension during pregnancy. The BUMP study surveyed 5,555 pregnant women from antenatal clinics in 16 hospitals in England and found that nearly half of the 389 hypertensive women reported the use of SMBP, and that the majority of them (79%) shared their BP readings with their treating doctor (129). The same author group also conducted the OPTIMUM-BP trial in 2019, an unmasked randomised controlled trial comparing SMBP intervention versus usual care for the management of HDP. A total of 86 women with chronic hypertension and 72 with GH from four UK centres were randomised (2:1) to intervention (SMBP) and control (usual care) (130). The authors reported that participants persisted with the intervention for 80% or more of their time from enrolment until delivery, with 86% (43/50) and 76% (38/49) of those having chronic and gestational hypertension,

respectively. They concluded that a larger randomised control trial would be essential (130) to make the place of self-monitoring in pregnancy clearer (129).

2.4.1.2 Severe Hypertension

All five guidelines (6,68-71, 75) are of the same view regarding the treatment of severe hypertension, stating that a BP level of this magnitude is considered a medical emergency and that BP needs to be lowered urgently, albeit carefully, to prevent cerebral haemorrhage and hypertensive encephalopathy. Steer et al. (131) reported that both low and high BP during pregnancy are associated with low birth weight and increased perinatal mortality; thus care should also be taken to avoid maternal hypotension and potential under perfusion of the placenta (6). Additionally, fetal heart rate monitoring is crucial whilst the mother is on treatment to lower severe BP, as maternal hypotension is associated with reduced fetal heart rate (6).

The guidelines, however, do differ in the definition of severe hypertension, especially the cut-off for systolic BP, as shown in Table 2.1. Moreover, target BP levels whilst on antihypertensives for severe hypertension are only mentioned in the Canadian (72) and American (83) guidelines. This inconsistency with international guidelines was the subject of a recent systematic review by Scott et al. who concluded that clinical recommendations should be consistent and inconsistencies including definitions of pre-eclampsia severity, biomarkers for prediction or time-of-disease assessment, and normalisation of blood pressure when mild to moderately elevated should be the focus of future research (132).

Another difference in recommendations is which antihypertensive agent to use as first line in severe hypertension. Table 2.3 summarises the slight differences in these recommendations.

Table 2.3: Comparison of first line antihypertensive agents for treatment of severe hypertension

Guideline	First line antihypertensive
SOMANZ 2014[6]	The most important consideration in choice of antihypertensive agent is that the treating unit has experience and familiarity with that agent.
ISSHP 2018[68]	IV hydralazine, IV labetalol or oral nifedipine
NICE 2019[69]	IV hydralazine, IV labetalol, oral nifedipine or oral labetalol
SOGC 2014[72]	IV hydralazine, IV labetalol or oral nifedipine
ACOG 2019[83]	IV hydralazine, IV labetalol or oral nifedipine

Other antihypertensive agents that have been used for the treatment of severe hypertension include diazoxide and glyceryl trinitrate (6, 19, 133). Sridharan and Sequeira conducted a network meta-analysis and trial sequential analysis of randomised clinical trials involving medications for treating

severe hypertension in pregnancy (133). They confirmed that nifedipine, hydralazine and labetalol have similar efficacy in the treatment of severe hypertension in pregnancy and that there is insufficient evidence for other medications (133).

2.4.1.3 Mild to moderate hypertension

The management of mild to moderate hypertension is an ongoing debate in the obstetric literature (134, 135). The main arguments in this debate are that, although antihypertensive medications may decrease the impact of elevated maternal BP on fetal and maternal outcomes, the medications themselves may impair fetal growth and perinatal health outcomes (134). The Chronic Hypertension and Pregnancy (CHAP) Project is an open-label randomised clinical trial (ClinicalTrials.gov Identifier: NCT02299414) which is currently recruiting to address this debate for women with mild chronic hypertension (130). CHAP has the primary aim to evaluate the benefits and harms of pharmacologic treatment of mild chronic hypertension in pregnancy (87). It is hoped that this trial will provide much needed evidence for this clinical debate.

For women with mild gestational hypertension or pre-eclampsia, the SOMANZ, ISSHP, NICE and SOGC guidelines recommend antihypertensive treatment when BP is ≥140/90 (6, 68, 69, 72). The ACOG guideline, however, only recommends antihypertensive treatment when the BP is severe (defined as SBP ≥ 160mmHg and/or DBP ≥ 110 mmHg as per ACOG) (70).

There is also controversy surrounding the target BP in women with mild gestational or chronic hypertension when treated with antihypertensives. El Guindy et al. evaluated the effects of tight versus a less tight control of mild hypertension during pregnancy (137). The goal of antihypertensive treatment in the 'less tight' group was a target BP of 130-139mmHg systolic and 80-89mmHg diastolic. The 'tight' group had a target BP of <130mmHg systolic and <80mmHg diastolic. The trial results suggest that tighter control of BP reduces antenatal hospitalisation without adversely affecting perinatal outcomes (137). The results are limited by the relatively small sample size (n=125) and the fact that only one antihypertensive agent, methyldopa, was used.

In an attempt to formally address this issue, the CHIPS (Control of Hypertension In Pregnancy Study) protocol and study group was instigated in 2007 (138) with the trial concluded in 2015 (13). CHIPS was an open, international, multicentre trial involving women at 14 weeks 0 days to 33 weeks 6 days of gestation who had non-proteinuric chronic or gestational hypertension, office diastolic BP of 90 to 105 mmHg and a live fetus. Women were randomly assigned to 'less-tight' control (target diastolic BP, 100 mmHg) or tight control (target diastolic BP, 85 mmHg). The composite primary outcome was pregnancy loss or high-level neonatal care for more than 48 hours during the first 28 postnatal days. The secondary outcome was serious maternal complications occurring up to 6 weeks postpartum or until hospital discharge, whichever was later (13). This trial was expected to inform this debate, but it

found no significant differences in adverse outcomes between 'less-tight' versus 'tight' control of hypertension. A higher incidence of severe hypertension, however, was observed in the less-tight group (13). Thus, the debate continues and the decision to treat mild to moderate BP remains with the clinician and their discretion.

Table 2.4 summarises the most commonly used first line antihypertensive medications during pregnancy, both in Australia and internationally.

Table 2.4: First line antihypertensive medication

Guideline	Labetalol	Methyldopa	Nifedipine	Oxprenolol^
SOMANZ 2014[6]	✓	✓	×	✓
ISSHP 2018[68]	✓	✓	✓	✓
NICE 2019*[69]	✓	×	×	×
SOGC 2014 [72]	✓	✓	✓	×
ACOG 2019[70]	✓	×	✓	×

*Nifedipine is recommended as the second choice, followed by methyldopa.

^ Oxprenolol has now been discontinued

Other antihypertensives used as second or third line include prazosin, clonidine and hydralazine (6, 19) (the safety of these agents is discussed in S 2.6.). A Cochrane review in 2018 found that labetalol, oxprenolol and nifedipine appear to be more effective than methyldopa for preventing severe hypertension (19).

Abalos et al. have performed successive Cochrane systematic reviews of randomised control trials investigating the effectiveness of antihypertensive use in mild to moderate hypertension since 2001 (139). Subsequent reviews were performed in 2007, 2014 and 2018 (19, 139, 141). The most recent review was inconclusive regarding the benefits of treatment of mild-moderate hypertension during pregnancy, confirming that treatment of mild-moderate hypertension does not influence progression to pre-eclampsia (19). Thus, the treatment threshold for mild-moderate hypertension remains in contention and is dictated by the choice of the treating clinician. The review, however, found that labetalol, oxprenolol and nifedipine appear to be more effective than methyldopa for preventing severe hypertension (19).

The adverse drug reactions and precautions/contraindications that are applicable to the general population are also taken into consideration when prescribing antihypertensives during pregnancy. The common adverse drug reactions as well as precautions and contraindications that are relevant to pregnancy and HDP are summarised in Table 2.5.

Table 2.5 : Considerations for selecting antihypertensives during pregnancy (*adapted from 6, 142)*

Antihypertensive	Dosage	Common adverse reactions	Precautions and contraindications
Labetalol	100-400mg every 8 hours	Postural hypotension, dizziness	Asthma Hyperthyroidism Bradycardia Pheochromocytoma
Methyldopa	250-750mg three times daily	Dizziness, headache, dry mouth	Depression Active hepatic disease Pheochromocytoma
Nifedipine	20mg -60 mg slow release up to twice daily	Dizziness, headache, flushing	Aortic stenosis
Oxprenolol*	20-160 mg every 8 hours	Postural hypotension, bradycardia	Asthma Hyperthyroidism Bradycardia Pheochromocytoma
Prazosin	0.5-5 mg every 8 hours	First-dose hypotension, dizziness	Aortic stenosis Volume depletion
Clonidine	75-300µg three times daily	Dizziness, headache, dry mouth	Depression Severe bradycardia
Hydralazine	25-50 mg every 8 hours	Flushing, headache, nausea	Idiopathic systemic lupus erythematosus or related diseases Hyperthyroidism Aortic stenosis

* Oxprenolol has now been discontinued

2.4.2 Prevention and management of pre-eclampsia

As mentioned in S 2.3.2.3, pre-eclampsia is a serious pregnancy disorder with multisystem involvement and high morbidity and mortality rates for both the mothers and the neonates. Prevention of pre-eclampsia involves close monitoring of women who are at risk of developing it. This monitoring includes: BP control, monitoring of proteinuria, liver function, epigastric pain, neurological symptoms and platelet count (6). Of particular risk of pre-eclampsia are women with pre-existing chronic hypertension (109). The ISSHP 2018 guidelines (68) are the only guidelines that recommend that all women with chronic hypertension in pregnancy have standard tests performed at the start of their pregnancy or when hypertension is diagnosed before 20 weeks gestation. This provides a baseline reference should suspicion arise later in pregnancy of superimposed pre-eclampsia, which will complicate up to 25% of these pregnancies (68, 108).

The recommended tests are as follows:

1. A full blood count (haemoglobin and platelet count).

2. Liver enzymes (aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase) and function tests (international normalised ratio, serum bilirubin, and serum albumin).

3. Serum creatinine, electrolytes and uric acid.

4. Urinalysis and microscopy, as well as protein:creatnine or albumin:creatinine ratio.

5. Renal ultrasound if serum creatinine or any of the urine tests are abnormal (68).

Furthermore, a recent expert review by Battarbee et al. on chronic hypertension and its management recommended that antihypertensive medication should be altered to achieve optimal BP control (143). They recommended similar baseline laboratory tests to those recommended by ISSHP early in pregnancy, but recommend them preconception (143).

Chahine and Sibai, who are experts in the field of chronic hypertension in pregnancy, recommend stratifying women with chronic hypertension as high or low risk to better inform clinicians about thresholds to initiate antihypertensive therapy, target BPs, frequency of antenatal visits and timing of delivery (87). Based on their definition, women classified as high risk include those with either secondary hypertension, age >35 years, target organ damage, severe range SBP or DBP (SBP ≥160mmHg and/orDBP≥110mmHg) or requiring two or more antihypertensive medications to control BP (87). These women require stricter BP control and more frequent follow-up visits, as their associated rates of adverse maternal and/or fetal outcomes appear higher than women classified as low-risk chronic hypertension (87).

Low-dose aspirin (75-100mg daily) is the only pharmacological treatment that has strong evidence for the prevention of pre-eclampsia (101). Duley et al. performed a Cochrane review of the evidence available for the effectiveness of low-dose aspirin in the prevention of pre-eclampsia in 2019 (144). The authors concluded that there is high-quality evidence that low-dose aspirin taken daily from the end of the first trimester (completion of 12 weeks gestation) until 36 weeks' gestation reduces the risk of developing pre-eclampsia by around 18% (relative risk 0·82; 95% CI 0·77–0·82) (144). Prior to this, in 2010, Bujold et al. published a landmark meta-analysis of placebo-controlled randomised clinical trials that suggested starting aspirin ≤16 weeks' gestation is effective in preventing pre-eclampsia, while there was no statistically significant effect when aspirin was commenced >16 weeks' gestation (14). The same author group followed this up with a meta-analysis of studies related to the effectiveness of low-dose aspirin in the prevention of perinatal death and adverse perinatal outcome, concluding that starting aspirin ≤16 weeks' gestation is effective in preventing these adverse outcomes (145). Rolnik et al. performed the ASPRE trial, a multicentre, double-blind, placebo-controlled trial, randomly assigning 1,776 women with singleton pregnancies who were at high risk for pre-term pre-eclampsia to receive aspirin, at a dose of 150 mg per day, or placebo from 11 to 14 weeks of gestation until 36 weeks of gestation (146). They concluded that treatment with low-dose aspirin was more effective than placebo to reduce the incidence of pre-term pre-eclampsia in women at high risk of this diagnosis (146). On the basis of these three publications, the recommendation to administer low-dose aspirin to pregnant women at risk of pre-eclampsia ≤16 weeks' gestation was added to all of the five main clinical guidelines (101).

Calcium supplementation is another commonly used preventative agent for pre-eclampsia. The SOMANZ, ISSHP and SOGC guidelines recommend at least 1g daily (1.0–2.5g/d) of supplemental calcium in addition to low-dose aspirin in women at high risk of developing pre-eclampsia and have low dietary calcium intake (<600mmHg/d) (6, 68, 72). ISSHP goes further to recommend that it is reasonable to give calcium when intake cannot be assessed or predicted (68). The ACOG guidelines do not make this recommendation as they state that low baseline dietary calcium is not common in the US (70). The NICE guidelines also do not mention calcium supplementation (69). Hofmyer et al. performed an updated systematic review of 27 randomised controlled trials (including cluster-randomised trials) in 2018, comparing high-dose calcium supplementation (at least 1 g daily of calcium) during pregnancy with placebo for the prevention of pre-eclampsia (147). The authors concluded that 1g of calcium daily reduced rates of pre-eclampsia (RR 0·45; 95% CI 0·31–0·65) (147).

The recent understanding of the role of angiogenic markers in the pathophysiology of pre-eclampsia, as described in S 2.3.2.3, has opened the door to several potential treatment targets for the prevention of pre-eclampsia. Some of these potential preventative treatments include low molecular weight heparins (148-150), metformin (151), pravastatin (152), sulfasalazine in combination with

esomeprazole (153) and general proton pump inhibitors (154). Many of these studies are in their early stages and larger trials will be required before either of these medications become part of standard clinical practice. Additionally, experts in the field hope that one of these medications or a new pharmaceutical agent may be able to slow the progression of pre-eclampsia, a goal described by experts in the field as transformative (101). Furthermore, the understanding of biomarkers has allowed the pursuit of active strategies to predict which women are at high risk of developing pre-eclampsia via a screening test using the sFlt1/PlGF ratio (117). This test also has the potential as a diagnostic tool to exclude the likelihood of pre-eclampsia in women with severe uncontrolled hypertension (117).

2.4.3 Fetal surveillance

Regular fetal surveillance is recommended to all women with HDP to monitor fetal growth and wellbeing (6). This monitoring is done at each antenatal appointment. Additionally, fetal surveillance via a pregnancy day assessment unit has been found to be associated with good perinatal outcomes in women with various obstetric complications, including women with well controlled hypertension (6). Assessing growth trends by serial ultrasound is recommended to monitor for signs of IUGR leading to fetal growth restriction (FGR) (6). The comparison of fetal growth is measured by centiles. The SOMANZ guidelines recommend that this is done via a customised centile chart (6) that takes into account the mother's age, ethnicity, weight at conception, as well as the gender of the fetus and the gestational age in days (155). Mongelli and Gardosi developed a customised centile chart calculator for the Australian population in 2007 (155) and was used at the study sites that were researched for this thesis, and thus in the analysis of the results. FGR is defined as $<10^{th}$ centile on this scale (6). FGR can warrant early delivery if it is severe and there is no evidence of further growth in-utero (6).

2.4.4 Timing of delivery

The timing of delivery is dependent on the severity of the hypertensive disease, the wellbeing of the fetus and the gestational week of pregnancy. The aim is to prolong the pregnancy to as close to term (37 weeks) as possible (6). There are cases, however, where immediate delivery is required to prevent major adverse outcomes, including maternal or fetal death (6). These include severe uncontrolled BP, major involvement of any organ in pre-eclampsia, HELLP or severe fetal compromise (6). The timing of delivery in this case would depend on the urgency of the situation. All five guidelines agree on this premise (Table 2.6).

Table 2.6: Outline of viable delivery options and recommendations for transfer(6)

Gestation at onset	**Previable <23 weeks and 6 days**	**24 weeks-31 weeks and 6 days**	**32 weeks-36 weeks and 6 days**	**37 weeks onwards**
Delivery plan	Consult with tertiary institution: likely to need termination of pregnancy or extreme pre-term delivery. High risk patient.	Consult and transfer to Tertiary institution: likely to need pre-term delivery. Aim to prolong pregnancy where possible.	Aim to prolong pregnancy where possible, deliver in institution with appropriate paediatric care.	Plan delivery on best day in best way

Chronic hypertension is associated with up to a three-fold risk of perinatal death compared with singleton, normotensive pregnancies, even when it is mild-moderate (156). The SOMANZ guideline therefore recommends that appropriate monitoring of these women to the end of the pregnancy is mandatory (6). Ram et al. conducted a retrospective population-based study of women with chronic hypertension who had a singleton hospital birth at 38 weeks of gestation and beyond in Ontario, Canada, between 2012 and 2016 (157). Their findings suggest that, in women with isolated chronic hypertension, induction of labour at 38 or 39 weeks of gestation may prevent severe hypertensive complications without increasing the risk of caesarean delivery (157).

The timing of delivery in women with mild gestational hypertension or pre-eclampsia is generally agreed upon among the guidelines. A recommendation of delivery as soon as practicable after the completion of 37 weeks gestation is made (by all except ISSHP) to prevent progression to severe hypertensive disease. The main trial that influenced the unity of this decision was the 'Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation' (HYPITAT) trial published in 2009 (158). The HYPITAT was a landmark, multicentre, unblinded randomised controlled trial comparing outcomes after induction of labour and expectant monitoring in 756 pregnant women with mild gestational hypertension or mild pre-eclampsia between 36 and 41 weeks gestation (158). The study reported that immediate induction of labour was associated with a reduction in the incidence of severe hypertension, without an increase in the caesarean section rate (158). Furthermore, some experts in the field, such as Chappell et al. specifically recommend that delivery is warranted at 37 weeks gestation or beyond, because expectant management will increase the likelihood of adverse maternal outcomes with little or no fetal gain

(101). The HYPITAT trial was followed up by a second trial published in 2015 which found that expectant management of women with mild gestational hypertension or pre-eclampsia between 34 and 37 weeks was associated with a non-significant increase in maternal adverse outcomes, but a significant reduction in neonatal respiratory distress (159). The findings cemented the recommendation for delivery after 37 weeks gestation in the above-mentioned guidelines.

Although these facets of management are now mostly well documented in the obstetric literature, some differences still remain in guideline recommendations as illustrated above. Moreover, there is a paucity of studies examining the nature of clinical management of HDP, especially in Australia.

2.5 Adverse outcomes of hypertensive disorders of pregnancy

2.5.1 Pregnancy, delivery and perinatal complications

Elevated BP during pregnancy has been associated with significant maternal morbidities, many of which are interlinked with perinatal complications. These include an increase in pre-term birth, premature separation of the normally implanted placenta before delivery (known as placental abruption), caesarean deliveries, emergency deliveries, IUGR, small-for-gestational age (SGA) and stillbirth (160,161). An increased incidence of congenital malformations has also been reported (161). Pre-term birth is defined as delivery before 37 weeks gestation (6). More specifically, the gestational week of pre-term delivery is defined as follows (162):

- **Late pre-term:** born between 34 and 36 completed weeks of pregnancy
- **Moderately pre-term:** born between 32 and 34 weeks of pregnancy
- **Very pre-term:** born at less than 32 weeks of pregnancy
- **Extremely pre-term:** born at or before 25 weeks of pregnancy

There have been many studies related to the incidence of these adverse pregnancy outcomes in pregnant women with HDP, either about HDP as a whole or specific HDP subtypes (161,163-166). The studies varied in whether they compared between women with HDP and women with normotensive pregnancies, sample size and statistical power (163-165). A meta-analysis published in 2021 reported that extents of association varied between studies, with some studies contradicting the findings of prior published studies (166). There were two prior meta-analysis. In 2014, Bramham et al. estimated the birth prevalence of several adverse outcomes only among women with chronic hypertension (166). The authors did not assess the risk of these outcomes associated with HDP by comparing with normotensive women (166). Mulualem et al. performed a systematic review in 2019, but only estimated the risk of pre-term birth associated with HDP in Ethiopia (167). In the context of the insufficient statistical power in primary studies and the shortage of previous reviews, Li et al.

recently conducted a meta-analysis of cohort studies to review and summarise the epidemiologic evidence on the association between HDP and risk of specific adverse outcomes in offspring, and to identify potential heterogeneity moderators by subgroup and sensitivity analysis (161). Table 2.7 summarises the findings of Li et al. (161).

Table 2.7 Meta-analysis of association between hypertensive disorders of pregnancy and adverse pregnancy outcomes *adapted from (161)*

Adverse outcome	Number of included studies	Odds ratio (95% CI)
Intrauterine growth restriction	30	5.476 (3.883-7.722)
Small-for-gestational age	49	3.389 (2.859-4.017)
Congenital malformations	12	2.655 (1.863-3.784)
Pre-term birth	75	4.195 (3.586-4.907)
Very pre-term birth	11	3.262 (1.9200-5.544)
Stillbirth^	16	1.928 (1.379-2.696)

^ Fetal death before or during labour after 20 weeks of gestation (154).

Common immediate complications of pre-term birth include SGA, laboured breathing or respiratory distress (due to compromised lung maturity) and lack of reflexes for sucking and swallowing, leading to feeding difficulties (162). The severity of these symptoms depends on the timing of the birth, with each additional week providing an extra opportunity for fetal growth and lung maturity. As such, prolonging the pregnancy to as close to term as possible is an important aspect in HDP management (6). It is recommended that, if a pre-term delivery before 34 weeks gestation is warranted, delivery should be delayed for at least 24-48 hours, if maternal and fetal status permit, to allow fetal benefit from antenatal corticosteroids (betamethasone or dexamethasone administered intramuscularly to the mother) for lung maturation. Additionally, before 32 weeks gestation, magnesium sulphate is administered antenatally to provide neonatal neuroprotection (6, 101). Unfortunately, up to 40% of women presenting with pre-eclampsia at less than 34 weeks gestation are ineligible for this prolongation of delivery as they are at higher risk of developing severe pre-eclamptic features including HELLP syndrome, placental abruption and eclampsia (6, 168-170). Magnesium sulphate is also recommended for the prevention of seizures in women with pre-eclampsia showing significant neurological signs and symptoms such as severe, intractable headache or repeated visual scotoma (6,101). The landmark Magpie Trial in 2002 showed that magnesium sulphate reduces the risk of an eclamptic seizure in women with pre-eclampsia by 58% and has thus been recommended as preventative eclampsia treatment (171).

Placental abruption is a serious fetal complication of HDP that increases the risk of stillbirth (6). Fetal testing cannot predict placental abruption, but good control of BP and avoidance of severe

hypertension can reduce the risk (6). An emergency caesarean delivery is required in the case of abruption. Other reasons for an emergency delivery in women with HDP include worsening pre-eclampsia, severe uncontrollable hypertension, IUGR and fetal distress. This can either be by induction of labour (IOL) or caesarean section depending on the urgency of the delivery and the mother's circumstances (6).

Pregnant women with chronic hypertension are at increased risk of adverse pregnancy outcomes (143, 172, 173). The risk of placental abruption is increased among women with chronic hypertension, especially when presented in association with uncontrolled hypertension and FGR (90, 173). Panaitescu et al. (174) performed a prospective screening study of adverse pregnancy outcomes in women with singleton pregnancy attending their first routine hospital visit at 11 weeks to 13 weeks and 6 days gestation in the UK. The authors found that women with chronic hypertension are also at increased risk for caesarean delivery compared with women without chronic hypertension (174). Moreover, women with chronic hypertension are at a five-fold risk for maternal death, peripartum cardiomyopathy, cerebrovascular accident, pulmonary oedema or renal failure (143). Bramham et al. performed a meta-analysis of 55 studies regarding adverse pregnancy outcomes in women with chronic hypertension (166). These studies included 795,221 pregnancies from 25 countries and spanned four decades and confirmed that chronic hypertension is associated with adverse pregnancy outcomes (166). The pooled average incidence, across study populations, of caesarean section, pre-term delivery, perinatal death and neonatal unit admission were all significantly higher in US studies of women with chronic hypertension than in the general US pregnant population (166). As early as 1983, Sibai found that the increased rates of maternal and fetal adverse outcomes in pregnant women with mild chronic hypertension are related not only to hypertension but also to factors relating to superimposed pre-eclampsia (90). Based on these findings, Sibai has advocated for closer monitoring of pregnant women with chronic hypertension (90).

In addition to the aforementioned adverse pregnancy outcomes associated with HDP, pre-eclampsia, especially when it develops severe features, presents an increased risk of additional morbidities, including acute renal dysfunction, hepatic haematoma or rupture, coagulopathy and pulmonary oedema (101). These severe features are often associated with pre-term pre-eclampsia (6, 175). Mooney et al. conducted a retrospective cohort study in 108 women presenting with pre-term pre-eclampsia at a tertiary hospital in Melbourne, from 23 weeks to 32 weeks and 6 days gestation, to examine the reason for delivery (maternal or fetal) and assess whether disease characteristics at presentation are predictive of delivery indication (175). The authors found that more participants were delivered for maternal indications (65.7%) compared to those requiring delivery on grounds of fetal compromise (19.4%) or for both indications (14.8%) (175). They also reported that women who delivered on maternal grounds were delivered at earlier gestation, had higher BP and higher incidence of abnormal liver function tests than those delivering for fetal indications (175). Other researchers in

the field of pre-eclampsia have developed prognostic tools to predict and stratify a pregnant woman's risk of adverse pregnancy outcomes and aim to tailor close surveillance for women at highest risk, so that delivery can be timed optimally (176, 177); however, these tools are not widely used in practice as of yet.

2.5.2 Long-term adverse outcomes of HDP

2.5.2.1 Long term adverse outcomes for the mother

Women with a history of HDP have a higher risk (nearly double) of developing future cardiovascular disease (CVD) in comparison to women who were normotensive during pregnancy (178, 179). It is thought that this could be a combination of the HDP and predisposition to CVD (180). The main CVD risk consistently linked with gestational hypertension and pre-eclampsia is future chronic hypertension (179, 181). Giorgione et al. performed a systematic analysis researching the incidence of postpartum hypertension within two years of a pregnancy complicated by HDP (182). They reported the risk of hypertension within two years of birth to be six-fold higher in women who experienced HDP, and that the augmented risk of hypertension after HDP is highest in the early postpartum period (182). Theilen et al. performed a retrospective cohort study to determine whether recurrent HDP is associated with increased mortality risks and found that there are excess risks for early all-cause mortality and some cause-specific mortality, which increased further with recurrent disease (183). A recently published data linkage study of 528,106 births in New South Wales, Australia, from 2002 to 2016 found that the ten-year absolute risk of hospitalisation or death from a cardiovascular event (ischaemic or hypertensive heart disease or stroke) was 2.1 per 1,000 for women without HDP, and 5.5 per 1,000 after HDP (184). The risk increased over time, with the risk for women with late-onset HDP (after 34 weeks gestation) increased 1.8 times (95% CI 1.4–2.2) at five years, 5.0 times (95% CI 4.1–5.8) at ten years and 11.8 times (95% CI 8.9–14.7) at 15 years postpartum, compared to women without previous HDP (184).

Leon et al. performed a large population-based cohort study using linked electronic health records from 1997 to 2016 to recreate a UK population-based cohort of 1.3 million women, with nearly 1.9 million completed pregnancies to study the association between HDP, pre-eclampsia and subsequent diagnosis of 12 different cardiovascular disorders (185). A total of 18,624 incident cardiovascular disorders were observed, 65% of which had occurred in women under 40 years (185). Compared to women without hypertension in pregnancy, those who had one or more pregnancies affected by HDP had a consistent hazard ratio of around 2.0 for any cardiovascular events such as stroke, cardiac atherosclerotic events, peripheral events, heart failure, atrial fibrillation and death, while the hazard

ratio for chronic hypertension was 4.47 (185). The authors also reported similar patterns of association for HDP, while pre-term pre-eclampsia conferred slightly further elevated risks (185).

Behrens et al. performed a population-based cohort study to compare rates of cardiomyopathy in women with and without a history of HDP (186). They reported that women with a history of HDP, compared with women with normotensive pregnancies, had a small but statistically significant increased risk of cardiomyopathy more than five months after delivery (186).

Pre-eclampsia alone has been linked to an increase in the risk of later major chronic conditions including cardiovascular, renal and neurological conditions (101). Chappell et al. state that it is plausible that the maternal vascular and organ injury caused by pre-eclampsia induces permanent physiological and metabolic rewiring that increases their predisposition to these chronic diseases (101). Several observational studies, systematic reviews and meta-analyses have been published about this (185, 187-189). The first systematic review was by Bellamy et al. in 2007 (187). The authors reported that pre-eclampsia increased the risk of chronic hypertension, ischaemic heart disease and stroke later in life (187). Around the same time, Ray et al. performed a population-based retrospective cohort study and found the risk of cardiovascular complications later in life to be greater in early onset pre-eclampsia, and pre-eclampsia that resulted in stillbirth or SGA infants (190). McDonald et al. performed a systematic review and meta-analysis shortly after, confirming that women with a history of pre-eclampsia or eclampsia have approximately double the risk of early cardiac, cerebrovascular and peripheral arterial disease, and cardiovascular mortality when compared to women who had normotensive pregnancies (188). More recently, researchers have defined the future cardiovascular risks of pre-eclampsia in more detail. A 2017 systematic review and meta-analysis by Wu et al. concluded that pre-eclampsia is associated with a 4-fold increase in future incident heart failure and a 2-fold increased risk in coronary heart disease, stroke and death (189). Moreover, women who have had pre-eclampsia have been found to be at a higher risk of developing future diabetes, even if they did not have gestational diabetes (191), and future chronic renal conditions (192, 193). There is also an increased risk of developing neurological conditions, such as vascular dementia and, potentially, an increased probability of developing deficits in perception, memory and motor function (194). The risks of developing many of these long-term complications rise more sharply if birth was pre-term, if there was coexistent FGR, if severe complications occurred, or if pre-eclampsia occurred in more than one pregnancy (183, 188).

2.5.2.2 Long term adverse outcomes for the offspring

A growing number of studies have reported the long-term effects on a baby born to a mother with HDP. The most common of these are neurodevelopmental disorders. Zwertbroek et al. on behalf of the HYPITAT-II author group, did a 2-year follow-up study of offspring born to mothers who gave birth between 34 and 37 weeks gestation (195). The authors found that early delivery in women with late pre-term hypertensive disorders is associated with poorer neurodevelopmental outcomes in their children at two years of age (195). Maher et al. performed a systematic review and meta-analysis researching the association between HDP and risk of neurodevelopmental disorders in the offspring (196). They found that exposure to HDP may be associated with an increase in the risk of autism spectrum disorder and attention-deficit/hyperactivity disorder (196). The risk of childhood hypertension has also been reported (197). Girls born to mothers who had HDP are also at increased risk of developing HDP during their future pregnancies (6).

2.6 Safety of antihypertensive medication during pregnancy

It is difficult to conduct well-designed randomised controlled trials to test the safety of antihypertensive medications during pregnancy due to ethical and safety reasons. It is also for these reasons that pregnant women are significantly under-represented in global clinical drug trials (198). Therefore, most of the safety recommendations are based on data from observational or population-based cohorts in women exposed to antihypertensives during pregnancy (17, 19). Furthermore, many of the antihypertensives commonly used in pregnancy are categorised as C in the Australian Drug and Evaluation Committee categorisation (Table 2.8), citing limited evidence regarding their safety in pregnancy.

Table 2.8: Australian Drug and Evaluation Committee categorisation of risk of antihypertensives during pregnancy

Category	Definition	Antihypertensive
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.	Methyldopa
B1	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or	

Category	Definition	Antihypertensive
	other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.	
B2	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.	Prazosin
B3	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.	
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.	Labetalol Atenolol Nifedipine Hydralazine
D	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.	Angiotensin converting enzyme inhibitors (ACEIs) Angiotensin II receptor antagonists and renin inhibitors
X	Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.	

The safety of methyldopa, labetalol, nifedipine and hydralazine have been confirmed over many years through the Abalos et al. systematic reviews (19, 139-141). A recent network meta-analysis by Bellos et al. investigating the comparative efficacy and safety of antihypertensive agents in pregnant women with chronic hypertension also confirmed this (17).

The impact of antihypertensive medications on IUGR has also been discussed. A landmark study by Butters et al. (199) found that atenolol when used for mild hypertension from the first trimester restricted intrauterine fetal growth. This prompted a change in the management of hypertension and brought the use of many other beta-blockers into question. This was reconfirmed in the review by Bellos et al. (17) who reported that atenolol was associated with significantly higher risk of small-for-gestational age compared with placebo (odds ratio, 26.00; 95% confidence interval, 2.61-259.29). Magee et al. reported that the effect of beta-blockers, other than labetalol and oxprenolol, on perinatal outcomes is uncertain and further trials are necessary to determine whether the benefits from using these medications to treat mild to moderate hypertension during pregnancy outweigh the risks to the fetus (200). Other studies have focused on the association between the antihypertensive-induced fall in mean arterial BP and the risk of infants with lower birth weights (201). An important point to consider is that hypertension during pregnancy can itself adversely affect fetal growth and increase the risk of pre-term births (68).

The question as to whether commonly used antihypertensive medications (methyldopa, labetalol, nifedipine and hydralazine) alter fetal or neonatal heart rate was reviewed Waterman et al. in 2004 (202). They ascertained that the available data are inadequate to conclude whether these medications adversely affect fetal heart rate or pattern (202). Magee and von Dadelszen, who were part of this author group in 2004 and are experts in the field of HDP, performed a thematic review of HDP management in 2018 and reported that this claim remains unsubstantiated and that changes in fetal heart rate or pattern should be ascribed to evolution of the underlying HDP, not to prescribed antihypertensive(s) (203). Research on congenital malformations due to commonly used antihypertensives has been scant (204); however, there is a somewhat larger amount of literature around the association of beta-blockers in general with congenital malformations (205, 206). Yakoob et al. performed a meta-analysis of observational studies investigating the risk of congenital malformations associated with exposure to beta-blockers early in pregnancy in 2013 (205). The authors reported that beta-blockers were not associated with major malformations overall, but were associated with three sub-types of malformations: cardiovascular defects (OR 2.0, 95% CI: 1.2, 3.4; four studies), cleft lip/palate (OR 3.1; 95% CI: 1.8, 5.4; two studies), and neural tube defects (OR 3.7, 95% CI: 1.2, 10.7; two studies) (205). Furthermore, > 80% of the studies that reported incidence of cleft palates and neural tube defects did not include labetalol treatment (205). Hence, the authors concluded that due to the small number of exposures and potential for bias, it is difficult to deduce causality between beta-blocker exposure (including labetalol) and fetal anomalies overall or within specific organ systems (205). Wu et al. performed a similar meta-analysis in 2020 and confirmed that beta-blocker use during early pregnancy is not associated with increased risks of overall congenital malformations or heart malformations (206); however, their ability to make robust conclusions was limited by wide confidence intervals for some organ-specific congenital malformations (206). Further

studies evaluating the associations between maternal use of beta-blockers and congenital malformations are warranted, as are studies of the effects of individual beta-blockers (and their dosages) on system-specific malformations (206).

2.7 Antihypertensive use during pregnancy

2.7.1 Adherence to medications in the general population

The last 50 years has witnessed periods of intensive clinical and research interest in medication taking (207). Similarly, the terminology used to describe the behaviour of patients and medication taking has also evolved. Compliance is defined as 'the extent to which a person's behaviour in taking medication, following a diet, and/or executing lifestyle changes corresponds with medical advice' (208). The literal definition of compliance, 'the reluctant acceptance of something without protest' or 'acquiescence' (209) implies that the practitioner is in an authoritarian role, giving recommendations without a regard for the individual patient. The term also exaggerates the practitioner's control over the process of taking medication (208). Various researchers have also considered the term compliance to be too closely related to blame of the patient and consider it detached from any consideration of the patient's health beliefs or goals (37). As a result of this discussion, the term 'adherence' has been utilised to reduce attribution of authoritarian power to the practitioner (210) and be less judgemental towards the patient.

Despite the extensive research into medication adherence, the WHO suggests that adherence to long-term treatment for chronic illnesses averages 50% in developed countries (37). One of the foremost researchers into medication adherence, Brian Haynes, suitably stated as early as 1976 'in an area where efficacious therapies exist or are being developed at a rapid rate, it is truly discouraging that one-half of patients for whom appropriate therapy is prescribed fail to receive full benefit through inadequate adherence to treatment' (211). Nonadherence refers to deviations from agreed treatment, either by under utilisation, over utilisation and/or general incorrect use of medication. Nonadherence is categorised into two broad types; 'intentional nonadherence' which involves a patient altering their dosage regimen to suit their own needs, is often associated with their beliefs about the medication and a 'decision balance' (39, 212) and 'unintentional nonadherence' which may be due to the patient forgetting to take the medication (39).

Adherence to medications is a multi-factorial issue. The WHO 2003 report, Adherence to Long-term Therapies: Evidence for Action (37), identified that the ability of patients to follow treatments is frequently compromised by more than one barrier. These barriers were divided into five categories: social and economic factors, therapy-related factors, patient-related factors, condition-related factors

and health system/health care team factors. Health beliefs and perceptions about the condition is another factor that can impact on adherence (27). The Ascertaining Barriers to Compliance (ABC) framework was derived from a systematic review of the medication adherence literature by Vrijens et al in response to the 'Adherence to Long-term Therapies: Evidence for Action' WHO 2003 report. This framework conceptualised medication adherence into different phases, namely initiation, implementation and persistence and provided standardised terminology of these terms in adherence research (213).

2.7.2 Adherence of the general population to antihypertensive medication

Adherence to antihypertensive medications has been studied widely since the early 1970s (214). Nonadherence to antihypertensives includes failure to initiate treatment, to take medications as often as prescribed, and to persist on therapy long-term (215). It is estimated that less than 50% of patients who are prescribed an antihypertensive remain on the treatment 1 year after initiation (216). Burnier and Egan (215) summarised the factors affecting nonadherence to antihypertensive agents in a review in 2019. They noted that although adherence literature has advanced since the publication of the WHO report, the five dimensions of adherence remain useful in explaining the factors related to nonadherence to antihypertensives in the general population (215). Adverse effects, complex dosage schedules and lack of understanding of the condition and its future health risks are some of the factors associated with poor adherence to antihypertensive medications in the general population (215).

2.7.3 Medication use and adherence to antihypertensive medication during pregnancy

Underpinning the optimal management of HDP cases that require antihypertensive treatment is adherence to the prescribed medication regimen. Despite the fact that many adherence studies in the general patient population with hypertension show poor adherence rates (215), there is scant research into the rate of adherence or lack thereof and the factors affecting adherence to antihypertensives in pregnant women. It is difficult to extrapolate adherence data from the general adult population to pregnant women. Whereas adult hypertension is a long-term risk factor where the goal of BP control is to prevent future cardiovascular events, hypertension during pregnancy in around 70% of cases is gestational (217) and is, by definition, a transient disorder that is often alleviated after delivery (6, 68). Similarly, studies that have explored the use of medications in pregnant women have tended to investigate prescription medication use in general with little focus on common drug classes such as antihypertensives. A study by Olesen et al. (218) found that adherence to medication for the treatment of chronic diseases, including diabetes and hypertension, during pregnancy was high (70-100%). On the other hand, in a cross-sectional, multinational web-based study about medication use in pregnancy by Lupattelli et al. (219), 32.9% of women self-reported low adherence to cardiovascular medications. Neither study (218, 219), however, specified the adherence rate for antihypertensives, nor did they

mention the sub-type of hypertension (i.e. chronic or gestational). A survey conducted by Sawicki et al. (54) in one Melbourne maternity hospital found that having hypertension slightly increased the likelihood of pregnant women's adherence to medication. There was, however, no further information on the users of antihypertensive medications, as the focus of the study was pregnant women with asthma. There is limited information surrounding adherence of pregnant women to antihypertensive medicines, which indicates a significant gap in the literature, given the extent of HDP in pregnancy.

2.7.4 Perceptions of pregnant women towards medication use

The perceptions of pregnant women towards medication use can provide valuable information about their adherence to medications. Sanz et al. (220) conducted a study investigating the perceptions of lay people (pregnant women and non-pregnant women) and health professionals (GPs, gynaecologists, medical students and medical interns) about the teratogenic risks of commonly used medications. The study was carried out in the context of fetal malformations and potential difficulties in evaluating the risks, which included: the high prevalence of medication use by pregnant women, the fact that pregnant women usually take more than one medication (which can complicate causality), the difficulties in recalling medication use in the first trimester after the birth of a child, and the overall low incidence of major malformations in the general population (estimated at 1-5%) (220). The authors found that pregnant women perceived safe medications as carrying a higher risk than non-pregnant women did. Pregnant women perceived the risks associated with the medications included in the questionnaire to be higher than by non-pregnant women and the physicians (220). This high and 'unrealistic' perception may lead to unnecessary abortions or nonadherence to medication. In addition, the perception of risk by the doctors in the study was often wrongly interpreted (220), potentially resulting in distorted advice being given to patients, hence increasing the likelihood of nonadherence (220). Widnes et al. also reported that pregnant women and physicians have an unrealistic perception of heightened risk from medications with potential teratogenic effects (221). The authors suggested that the empowerment of pregnant women with correct medication information may assist in having realistic expectations (221).

Nordeng et al. investigated the potential impact of risk perception on a pregnant woman's decision to take a medication, specifically paracetamol, amoxycillin and phenytoin (28). The Internet-based questionnaire was completed by 1,793 women, 866 of whom were pregnant and 927 were mothers of children below the age of five (including breastfeeding women). Most of the women overestimated the teratogenic risk associated with the medications (28). These results are consistent with the work by the Motherisk Program in Toronto, Canada, which also reported that the use of evidence-based counselling can reduce pregnant women's fear of taking medications (222). Mulder et al. investigated the perception of risk versus benefit of nine specific drug classes during pregnancy (paracetamol, antacids, antibiotics, antifungal medication, drugs against nausea and vomiting, histamine-2 receptor

antagonists/proton pump inhibitors, antidepressants, nonsteroidal anti-inflammatory drugs, and sedatives/anxiolytics) by giving examples of medication names from each drug class (223). The questionnaire was completed by 136 pregnant women at various stages of gestation and various parities. The authors found that the women were most afraid of having a child with a birth defect (35%), a miscarriage (35%), or their child developing an allergic disease (23%) as a result of general medication use (223). They also found that the women in their first trimester self-reported higher risk scores than those in the second or third trimester (223). Although women in the first trimester only accounted for 13.8% of the studied population (223), this does indicate that education about the risk versus benefit of a medication that is required during pregnancy should be carried out either pre-pregnancy or early in the first trimester.

Other researchers, including Butters et al. specifically explored pregnant women's attitudes and knowledge of the effects of commonly used medications on the fetus (29). A total of 514 self-administered questionnaires were completed by postnatal women during their hospital stay. Most of the women (85%) recognised that the fetus is most at risk of being harmed during the first trimester of pregnancy, although significantly more women in the unemployed group and the youngest age group (15-20 years) revealed that they did not know which stage of pregnancy would pose the highest risk (29). Rizk et al. also explored the knowledge and practices of 400 pregnant women in their third trimester towards medication ingestion (224). They reported that 81.5% of primigravid women had poor and inadequate knowledge of the risks that medications can pose to the fetus (224). Similar results were observed in 87.1% of women who previously had abortions. A study exploring pregnant women's beliefs about medications in Norway reported that most of the women believed that medications in general were helpful and safe to use, but were unsure about their safety during pregnancy (225). Although the authors mentioned that beliefs can influence a patient's decision to take a medication, they did not make a specific link between these beliefs and medication adherence. A more recent cross-sectional, multinational, Internet-based survey went further to explore the differences in medication beliefs between pregnant women using medication, or not, for chronic diseases (226). It has been suggested that decisions on medication use may be assessed subjectively based on the women's personal experiences, influence from 'significant others', as well as norms and expectations of a 'good mother' (227, 228).

An additional factor that could potentially alter pregnant women's perceptions towards medication is the presence of depression. Pregnancy is a major life event that is accompanied by many hormonal changes. Both these factors increase the susceptibility of pregnant women to experience a new onset of depressive symptoms, or the return of a previous depressed state (229, 230). Estimates of the prevalence of depression during pregnancy vary widely ranging from 8% to 51% (229). A review by Bennet et al. found that the proportion of women who experience depression during the first trimester of pregnancy is similar to that of the general female population whereas the incidence of depression

during the second and third trimesters is nearly double that rate (229). Depression during pregnancy has been linked to pre-eclampsia (231) and poor health behaviours (232). Poor health behaviours can potentially contribute to low adherence to maternal appointments, monitoring of their health status (e.g. measuring of BP) and the use of medication. Furthermore, there is a growing evidence that women intentionally cease their antidepressants before or during the pregnancy (233). In 2019, Kothari et al. conducted an observational study in Brisbane, Australia, to explore attitudes and decision-making by pregnant women regarding antidepressant and anxiolytic use during pregnancy (233). The authors found that 68% of the women who self-reported use of antidepressants/anxiolytic medications during their current pregnancy ceased this medication prior to or during the pregnancy (233). The most common self-reported reasons for cessation were perceived potential adverse effects to the baby, advice of health care professional or the absence of depressive symptoms (233).

2.7.5 Sources of information

Pregnant women use a variety of sources to obtain information during pregnancy and have been doing so even prior to the advent of the Internet (29, 234, 235). In the late 1980s in Australia, Butters et al. (29) reported that most of the information was gained through books and magazines aimed at pregnant women, followed by doctors, friends and family, and then midwives. Julsgaard et al. (33) reported that medication counselling prior to and especially during pregnancy may significantly reduce the risk of nonadherence to medications. The quality and accessibility of medication information can have a significant impact on their adherence.

The MAP (Medications in Adelaide during Pregnancy) study was conducted in South Australia during September 1999. It investigated various aspects of medication use during pregnancy using interviews conducted at the Women's and Children's Hospital in Adelaide. One of the published reports specifically reviewed the sources of advice on medication use in pregnancy and reasons for medication uptake and cessation during pregnancy (236). An earlier Australian survey published in 1990 (237) found that informal sources, including books and magazines, accounted for information obtained by 64% of the participants. Doctors were a source of information for 64%, whilst antenatal classes (usually delivered by midwives) were a source of information for 50% of participants. Henry et al. (236) reported that GPs were the most frequently consulted practitioners (59% of cases) for formal medication information. One-third (36.4%) of participants approached a pharmacist for drug information during pregnancy. In comparison, only 26% consulted their obstetrician/antenatal doctor. The most commonly reported non-formal sources of medication information were relatives/friends (56%), followed by books (41%) (236). These results shed light on the traditional understanding of information seeking in the Australian context.

In more recent times, the Internet has had a major influence on decision making during pregnancy (238). The Internet, with its large search engines, has been seen as replacing textbooks. Similarly, online forums aimed at pregnant women have largely replaced the magazines that were previously common. The difference, however, is that the postings on these forums are of various levels of authenticity (239). Despite this, many pregnant women accept these forums as a significant source of information as their posts can be anonymised and the environment is non-judgemental (239). Rouhi et al. performed a content analysis on 333 messages posted on a post-childbirth online forum in Australia. They found that postpartum discussions of childbirth and later complications can be supportive, but that ill-information may result in a barrier to safe and reliable health care (239). The authors concluded that women should be encouraged to have access to online forums, but that they should be moderated by healthcare providers who can notify participants when a problem requires support from a relevant health professional (239).

Tastekin et al. has published a systematic review of studies that described how the Internet affects decision-making in healthy pregnant women (238). Most studies reported the Internet as a source of information about pregnancy; the most commonly searched topics in search engines were pregnancy, development of the fetus, labour, neonatal health and nutrition (238). Additionally, the Internet was found to affect decisions about the type of delivery, medication use in pregnancy and physical activity (238). Tastekin et al. concluded that the use of the Internet had a positive effect on the decision-making processes of pregnant women, increased their awareness, and had a visible effect on this process (238). However, it is important to note that the women who were included in the studies were healthy and hence did not have concerns about the potential effects of medications during pregnancy or the progression of conditions such as HDP. Conversely, Denton et al. used a modified consensual qualitative research approach to analyse 1,728 comments posted on a popular Internet message board (Babycenter.com) about the safety of the use of six common psychotropic medications during pregnancy (235). The authors found that while many comments conveyed emotional support, or encouraged women to seek professional advice, others contained inaccurate and/or contradictory information, or harsh criticism (235). The authors recommended that health care professionals should address questions and concerns that women have about the safety of these medications and recognise how the social context of the Internet impacts the emotional health of pregnant women faced with these decisions (235). In the context of HDP, online websites run by health professionals and volunteers providing reliable information and offering online support for pregnant women with HDP are that of the Preeclampsia Foundation (https://www.preeclampsia.org/) and Australian Action of Pre-eclampsia (https://www.aapec.org.au/). There have not been any studies addressing the usage of these websites to date.

Medicine information services are another source of information for the pregnant population. In Australia, these are available through selected tertiary hospitals as well as the National Medicines Call

Centre. In 2016, Pijpers et al. published an analysis of calls between 1 September 2002 and 30 June 2010 to the Australian National Medicines Call Centre operated by clinical pharmacists of Mater Health Services, South Brisbane, to elucidate the type of questions that pregnant women ask (240). The authors found that enquiries by pregnant women were prompted most often by conflicting information, inadequate information or desire for a second opinion (240).

Another source of formal medication information is the Consumer Medicines Information (CMI) leaflets that are often provided to consumers, or via an online link, informing them about their medication. As early as the mid 1990's, Van Trigt et al. reported that pregnant women found such leaflets 'vague and useless' (241). They called for the improvement of pamphlets by making the information more accurate and understandable in the context of pregnancy. More recently, Brown et al. investigated the views and experiences of over 40 obstetric practitioners and hospital pharmacists working at the Women's and Children's Hospital in South Australia regarding their views on pregnancy and lactation advice in Australian Product Information (API) for four commonly prescribed medications (metronidazole, cephalexin, diclofenac and dexamethasone – framycetin sulfate – gramicidin ear drops) using semi-structured interviews (22). The authors reported that reliance on API can result in negative ramifications, especially when this information is used in the CMI (22). They also found that API recommendations were overconservative, outdated and unreflective of clinical practice (22). Furthermore, a review of the CMIs of the two most commonly used antihypertensive medications during pregnancy in Australia (methyldopa and labetalol) made no mention of their indication during pregnancy (23, 242). For methyldopa, it is stated 'tell your doctor if you are pregnant, intend to become pregnant…your doctor will discuss the possible risks and benefits of using methyldopa during pregnancy…' (242). This gives little concrete direction for the mother. The CMI for labetalol states in bold '**Do not take Presolol (labetalol) if you are pregnant.** Labetalol is not recommended for use during the first trimester of pregnancy as it may affect your developing baby. If it is necessary for you to take labetalol later in pregnancy, your doctor will discuss the risks and benefits of taking it' (23). Women reading this would likely to be wary of taking such a medication at any stage of their pregnancy, despite a discussion of risk versus benefit with the prescriber.

The variety of formal and informal sources of information available to pregnant women may contain conflicting information (234). Hämeen-Anttila performed a multinational Internet-based survey to investigate the extent to which pregnant women use multiple information sources and the consequences of conflicting information (234). A total of 7,092 responses were analysed, including those from Australian respondents, who reported receiving conflicting information more often than women in other regions, except for Eastern Europe (234). The authors reported that such conflicting information often led to anxiety and the decision to cease the medication (234). They also called for more accurate and uniform teratology information to be made available to the public (234). All of the

above mentioned studies suggest that health care professionals should be more proactive in asking their patients whether they have further questions and providing them with relevant information.

The community pharmacist is an accessible healthcare professional who may be able to provide clarity when it comes to conflicting information about medication safety during pregnancy. Ceulemans et al.'s narrative review summarising the evidence on pregnant women's beliefs, medication adherence in pregnancy, and community pharmacists' counselling during pregnancy (243) found that community pharmacists' counselling was insufficient: insufficient knowledge and limited access to reliable information were reported as main barriers hindering pharmacists from providing quality counselling on medication use during pregnancy (243). Recently, Shanmugalingam et al. carried out a mixed methods quantitative (n=122) and qualitative (n=6) survey of women with recent high-risk pregnancy necessitating antenatal prophylactic aspirin, including women who were at high risk of developing pre-eclampsia (244). They found that pharmacists were not confident with their knowledge regarding HDP, which can result in conflicting advice as observed in a study of adherence to aspirin in the prevention of pre-eclampsia by the same author group (245).

2.7.6 Summary and gaps in the literature

At the commencement of this PhD, after a thorough review of the literature, gaps were identified in the understanding of the management of HDP as well as medication use and adherence of pregnant women with this condition. Despite several national and international guidelines for the management of HDP, in-practice clinical management was not well documented, especially in Australia. Understanding in-practice management and identifying potential gaps may assist in optimising patient outcomes. Moreover, without a clear picture of the in-practice management, the study of medication use and adherence in this population is not complete. This would limit clinical relevance of the findings from this thesis.

Although extensive research has been done in understanding factors affecting adherence to antihypertensive medication in the general population, this has not previously been done in pregnant women with HDP. Similarly, whilst medication use in general pregnancy has been described, the use of medications for HDP, including antihypertensives and low-dose aspirin during pregnancy, has not been previously explored in depth.

It is important to note that research into the role of pharmacists in the field was not available at the commencement of this PhD and is still in its infancy. Pharmacists require further education and training to equip them with the knowledge required to provide quality counselling to women during pregnancy, especially women with HDP. Research into the field of management of HDP and medication use in this population from a pharmacists' point of view may assist in better contextualisation of this information, making it more relevant to the practice of pharmacists.

CHAPTER 3

RETROSPECTIVE COHORT STUDY OF THE MANAGEMENT OF HYPERTENSIVE DISORDERS OF PREGNANCY

3.1 Introduction

Chapter 2 provided an overview of the literature pertaining to current guidelines, challenges and evidence regarding the management of hypertensive disorders of pregnancy (HDP). Although there are several international guidelines for the management of HDP, controversies remain regarding certain key points of management, including the blood pressure level at which to initiate antihypertensive treatment in pregnant women with mild-moderate gestational or chronic hypertension, and regarding their timely delivery. Moreover, **Chapter 2** showed that there is limited research about the in-practice use of antihypertensive medications during pregnancy. Most research in this field focuses on specific aspects of the management such as threshold for treatment of hypertension during pregnancy, safety of antihypertensive medications during pregnancy, and the timing of delivery. Similarly, there are few published studies regarding the overall management of hypertensive disorders of pregnancy, especially in Australia.
This chapter reports the findings from research that has been undertaken on pregnant women with HDP with a focus on their management.

The aim of the study reported in this chapter was to evaluate compliance with the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) clinical guidelines for the management of hypertensive disorders of pregnancy in a large tertiary Australian maternity hospital.
The specific objectives were:

(i) To evaluate compliance with SOMANZ 2008 clinical guidelines for management of hypertension during pregnancy, specifically:
    a) thresholds for initiation of antihypertensive therapy;
    b) appropriateness of medication regimens;
    c) use of aspirin in women with known risk factors for development of PE;

(ii) To evaluate clinical uptake of findings from the HYPITAT trial (158) regarding induction of labour for women with gestational hypertension [GH] or pre-eclampsia [PE] at term; and

(iii) To describe obstetric and neonatal outcomes in women with chronic hypertension [CH], GH and PE according to antihypertensive treatment.

A retrospective cohort study was undertaken to examine the management of women with a hypertensive disorder of pregnancy who gave birth at one tertiary maternity hospital in the year 2010.

This retrospective study has been published in the **Australian and New Zealand Journal of Obstetrics and Gynaecology** and is reproduced below.

Appendices relevant to this chapter are appendix 1,2,3 and 4.

3.2 Published Manuscript: Helou A, Walker S, Stewart K, George J. Management of pregnancies complicated by hypertensive disorders of pregnancy: Could we do better? Aust N Z J Obstet Gynaecol. 2017;57:253-59.

Aust N Z J Obstet Gynaecol 2017; 57: 253–259

ANZJOG

DOI: 10.1111/ajo.12499

ORIGINAL ARTICLE

Management of pregnancies complicated by hypertensive disorders of pregnancy: Could we do better?

Amyna Helou[1], Susan Walker[2,3], Kay Stewart[1] and Johnson George[1]

[1]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Victoria, Australia

[2]Department of Perinatal Medicine, Mercy Hospital for Women, Melbourne, Victoria, Australia

[3]Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Victoria, Australia

Correspondence: Dr Johnson George, Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, 381 Royal Parade Parkville, Melbourne, Vic. 3052, Australia.
Email: johnson.george@monash.edu

Received: 29 April 2015;
Accepted: 29 May 2016

Background: Hypertensive disorders are among the most common medical problems in pregnancy. Compliance with clinical practice guidelines has potential to translate to significant maternal and perinatal health benefits.

Aims: To evaluate compliance with Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) clinical guidelines for management of hypertension during pregnancy.

Methods: Inclusion criteria: women with hypertension in pregnancy who gave birth at a tertiary obstetric centre in 2010. Compliance with SOMANZ guidelines was assessed, as well as uptake of findings from the 'Induction of labour versus expectant monitoring for mild gestational hypertension/pre-eclampsia after 36 weeks' gestation' (HYPITAT) trial.

Results: Of 5624 women, 516 (9.2%) were identified with hypertension (49 chronic hypertension (CH); 457 gestational hypertension (GH) or pre-eclampsia (PE)). Thresholds to diagnose hypertension and initiate anti-hypertensive treatment were consistent with SOMANZ recommendations. Among women with CH, only 12.2% were prescribed aspirin prior to 16 weeks as PE prophylaxis. Of women with PE, 37 (18.6%) had known risk factors for development of PE at the initial visit yet only nine (24.3%) received aspirin. Of the 244 women who met HYPITAT inclusion criteria at 36 weeks, 174 (77.7%) were managed expectantly; nine (5.2%) developed severe adverse outcomes.

Conclusion: Current management guidelines for hypertension treatment were generally followed, although aspirin prophylaxis was frequently overlooked, resulting in up to 19 excess PE cases. Uptake of recommendations from the HYPITAT trial was low; however, severe complications were fewer than expected. Overall, this suggests that clinicians appropriately weigh up the likely maternal risk compared to infant benefits of deferred delivery in each case, a key recommendation of HYPITAT-II.

KEYWORDS
chronic hypertension, gestational hypertension, HYPITAT, low-dose aspirin, SOMANZ

INTRODUCTION

Hypertensive disorders, a leading contributor to maternal mortality and morbidity, complicate approximately 10% of pregnancies in Australia.[1] Perinatal risks of maternal hypertension include fetal growth restriction (FGR) and premature birth, with attendant increase in morbidity and mortality.[1] The legacy of preterm birth and FGR is lifelong, with increased risks of

TABLE 1 SOMANZ guidelines for the management of hypertension during pregnancy

Guideline	Recommendation for initiation of treatment	Recommendation for antihypertensive medication	Use of low-dose aspirin and/or calcium for the pre-eclampsia prevention	Timely delivery of pregnant women with hypertensive disorders
Society of Obstetric Medicine of Australia and New Zealand 2008[3]	Reasonable to initiate treatment at 140–160 mmHg systolic and/or diastolic BP reaches 90–100 mmHg on more than one occasion Severe hypertension defined as ≥170/≥110 mmHg	Methyldopa Labetalol Nifedipine Prazosin Oxprenolol Hydralazine	Low-dose aspirin is indicated for the secondary prevention of pre-eclampsia in women at increased risk Calcium should be offered to women at increased risk of developing pre-eclampsia, especially those with low dietary intake	Women who are at ≥37 gestational weeks should be considered for delivery, especially if the BP is not under control, the presence of a sign of severe pre-eclampsia or restricted fetal growth/ non-assuring fetal status.
Society of Obstetric Medicine of Australia and New Zealand 2014[4]	In the absence of compelling evidence, treatment of mild-moderate hypertension in the range of 140–160/90–100 mmHg should be considered an option and will reflect local practice. Severe hypertension defined as ≥160/≥110 mmHg	Methyldopa Labetalol Nifedipine Prazosin Oxprenolol Hydralazine	Low-dose aspirin is indicated for women with at least moderate to high risk of pre-eclampsia, ie secondary prevention of pre-eclampsia in women at increased risk and in women with significantly increased risk in their first pregnancy. Calcium should be offered to women with moderate to high risk of pre-eclampsia, especially those with low dietary intake	Plan delivery in the best way on the best day in women who are at ≥37 gestational weeks

BP, blood pressure

neonatal and childhood morbidity, and increased health risks in adulthood.[2]

Optimising the management of hypertensive disorders in pregnancy is an important component of antenatal care. At the time of this study, the 2008 Society of Obstetric Medicine of Australian and New Zealand (SOMANZ) guidelines on management of hypertension in pregnancy were in use,[3] on which our institutional guideline for management of hypertension in pregnancy was based. In 2014, the SOMANZ guidelines were updated.[4] Key recommendations include use of aspirin with or without calcium to reduce the risk of pre-eclampsia (PE) in moderate to high-risk women; attention to blood pressure control and surveillance for development of superimposed PE and FGR. Clear endpoints have been identified for delivery in severe PE. These recommendations have largely been unchanged since the publication of the 2008 guidelines (Table 1),[3] with the exception of the threshold for treatment of severe hypertension and the timely delivery of women with mild-moderate hypertensive disease, in light of findings from the 'Induction of labour versus expectant monitoring for gestational hypertension or mild PE after 36 weeks gestation' (HYPITAT) trial.[5]

Aims

1 To evaluate compliance with SOMANZ 2008 clinical guidelines[4] for management of hypertension during pregnancy, specifically:
   a thresholds for initiation of anti-hypertensive therapy;
   b appropriateness of medication regimens;
   c use of aspirin in women with known risk factors for development of PE;
2 To evaluate clinical uptake of findings from the HYPITAT[5] trial regarding induction of labour for women with gestational hypertension (GH) or PE at term; and
3 To describe obstetric and neonatal outcomes in women with chronic hypertension (CH), GH and PE according to anti-hypertensive treatment.

MATERIALS AND METHODS

Antenatal records were electronically retrieved for women who gave birth in 2010 at the Mercy Hospital for Women and had an International Classification of Diseases (ICD)-10 code[6] recorded for any hypertensive disorder during pregnancy. The diagnostic criteria for GH, CH and PE were based on the SOMANZ 2008 guidelines.[3] Records were manually reviewed (by AH) and relevant data were extracted. Maternal data included demographics, medical and obstetric history, progression and management of hypertension, including development of: moderate to severe hypertension (systolic blood pressure (BP) ≥ 150–170 mmHg and/or diastolic BP ≥ 100–110 mmHg),[3] severe hypertension (systolic BP ≥ 170 mmHg and/or diastolic BP ≥ 110 mmHg)[3] and PE.[3] Use of aspirin and time of initiation were recorded. Neonatal data included gestational age at delivery, birthweight and need for special or neonatal intensive care admission. Customised centiles were calculated and FGR recorded if birthweight was less than the tenth customised centile. Centiles were

calculated using the calculator devised by Mongelli *et al*[7] specifically for the Australian population, allowing adjustment for maternal characteristics such as height and weight, gestational age and fetal gender.

Among women who reached 36 weeks gestation with mild GH or PE and a single fetus in a cephalic presentation, outcomes were compared between those managed expectantly and those managed with immediate/as soon as practicable induction of labour (IOL), as described in the HYPITAT trial.[5] Outcomes compared between groups were those reported in HYPITAT, namely maternal mortality, maternal morbidity (eclampsia; haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome; pulmonary oedema; thromboembolic disease; and placental abruption), progression to severe hypertension or proteinuria, and major post-partum haemorrhage (>1000 mL blood loss).[5]

Data were analysed using descriptive statistics and appropriate univariate analysis (one-way analysis of variance, Kruksal–Wallis, Mann–Whitney *U*-tests and Student's *t*-tests) using SPSS (version 21.0, IBM, New York, NY, USA). $P < 0.05$ was considered statistically significant. *Post hoc* comparisons were done using Bonferroni test. Human Research Ethics Committees of Mercy Health and Monash University approved the study.

RESULTS

Of the 5624 women who gave birth at MHW in 2010, 602 (10.7%) had an ICD code for hypertension. Of these, 86 were excluded as they did not meet the SOMANZ criteria for hypertension in pregnancy (Fig.1). The number of women included in the analysis was 516, resulting in 524 babies (eight sets of twins). Participants were classified into groups: CH (treated and untreated) (n = 49); GH (treated and untreated) (n = 268) and PE (n = 199). The CH treated group includes women with CH who were receiving treatment during pregnancy regardless of initiation pre-pregnancy or during pregnancy. The CH untreated group includes those who did not receive treatment at any time during pregnancy. Demographic and obstetric details are summarised in Table 2.

Management of pregnancies at term (36 weeks and beyond) with mild hypertension during pregnancy

Of the 355 women with mild GH or mild PE, 224 (63.1%) had not been delivered at 36 weeks and had no contraindication for IOL, such as breech or planned caesarean. Of these, 50 (22.3%) were

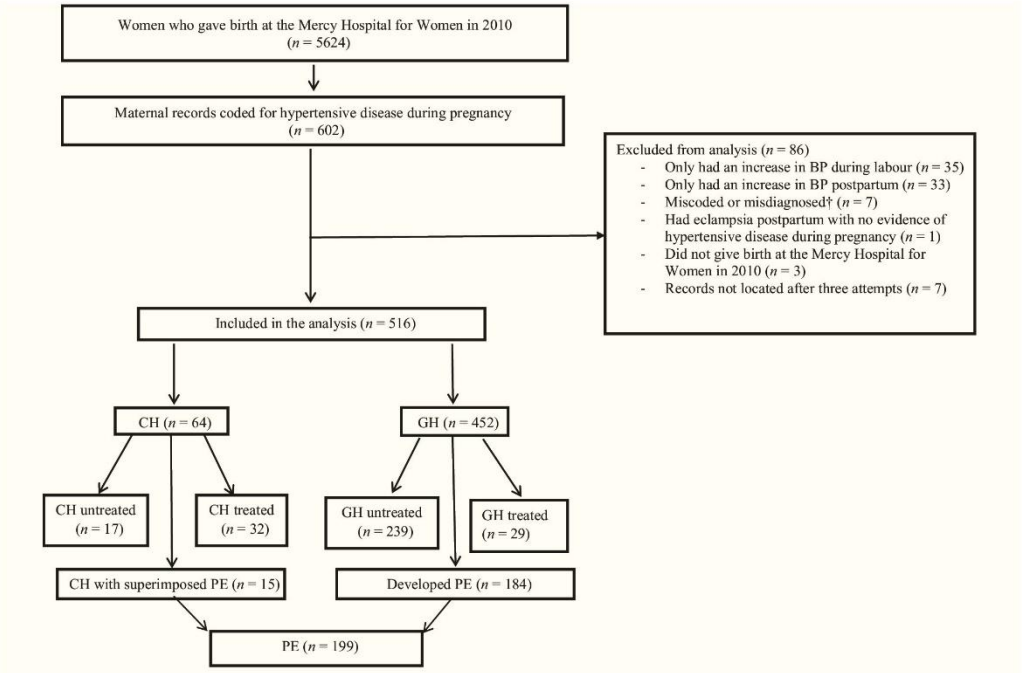


FIGURE 1 Patient selection flowchart. †Failed to find a recorded diagnosis of hypertensive disease in the medical record. BP, blood pressure; CH, chronic hypertension; GH, gestational hypertension; PE, pre-eclamspia.

TABLE 2 Baseline maternal demographics and obstetric history (n = 516)

Characteristic	CH untreated (n = 17)	CH treated (n = 32)	GH untreated (n = 239)	GH treated (n = 29)	PE (n = 199)
Age (years), mean ± SD	31.82 ± 4.44	34.26 ± 5.61**,**[1]	30.89 ± 5.22**	32.64 ± 5.22	30.73 ± 5.32**[1]
BMI, median (IQR)	32 (24–38)*,*[1],*[2]	31 (25–37)	28 (24–34)*	27 (26–30)*[1]	27 (24–33)*[2]
Nulliparous, n (%)	8 (47.1)	15 (46.8)	140 (58.6)	22 (75.9)	123 (61.8)
Current smoker, n (%)	1 (5.9)	6 (18.8)	20 (8.4)	3 (10.3)	22 (11.1)
Existing indication for low-dose aspirin, n (%)¶	17 (100)	32 (100)	28 (11.7)	0	37 (18.6)
Prescribed low-dose aspirin, n (%)	2 (11.8)†	4 (12.5)‡	6 (21.4)	0	9 (24.3)§
Gestational week of initial visit, median (IQR)	11 (8–14)	10 (8–13)	15 (11–16)	0	12 (10–16)

,[1],*[2]P = 0.03; **,**[1]P < 0.01. [1,2]Groups which are being compared.
†One woman was also prescribed calcium;
‡two women were also prescribed calcium;
§four women were also prescribed calcium;
¶based on the SOMANZ guideline for the management of hypertension in pregnancy 2008. BMI, body mass index; CH, chronic hypertension; GH, gestational hypertension; IQR, interquartile range; PE, pre-eclamspia

managed with immediate/as soon as practicable IOL, while 174 (77.7%) were expectantly managed. Progression to severe hypertension and to severe PE were the only relevant adverse outcomes in this group. The proportion of women who developed a composite severe adverse outcome, as defined by HYPITAT,[5] was 4.0% in the immediate management group and 5.2% in the expectant management group, rates that were not significantly different. There was no significant difference in the rate of caesarean section between these groups. The FGR (< tenth centile) rate was 9.2% in the expectant management group and 14% in the immediate management group. However, there was no significant difference in the customised centile between the two groups (44.9 (±28.7) and 49.6 (±30.4) in the immediate and expectant management groups, respectively).

Thresholds for diagnosis of hypertension and initiation of treatment

Treatment was initiated at mean systolic BP 154 mmHg and diastolic BP 97 mmHg. BP at initiation of treatment did not differ among the three groups (Table 3). Women prescribed treatment for hypertension (with GH or PE; n = 125), were more likely not only to be diagnosed at higher systolic and diastolic BP, but also at an earlier gestation than those with untreated GH or PE.

Medication prescribing patterns for hypertension during pregnancy

Among women with CH, methyldopa was first-line treatment in 62.5%, followed by labetalol in 31.3%. Other agents included nifedipine, phenoxybenzamine and metoprolol XL. Three (9.4%) required multiple anti-hypertensive agents. Among women with GH, labetalol was first-line treatment in 79%, followed by methyldopa in 13.8%. Two (6.9%) were prescribed nifedipine as an additional agent. Among women with PE, labetalol was prescribed in 71.4% and methyldopa in 59.1%. Twenty-five (37.9%) required multiple antihypertensive agents; 13.7% were treated with other agents, including nifedipine, hydrazaline, verapamil and magnesium sulphate.

Use of low-dose aspirin and/or calcium in women with moderate to high risk of pre-eclampsia

Of the 49 women who had CH at the initial visit, only six (12.2%) received low-dose aspirin, two of whom also received calcium supplementation, at gestation <16 weeks (Table 2). Two women commenced aspirin after 16 weeks. Mean gestation at initiation of therapy was 10 weeks and three days. Of those who developed hypertension during pregnancy (GH and PE), 65 (13.9%) had an indication for low-dose aspirin at the initial visit, most commonly past history of PE (84.6%), renal disease (3.1%), systemic lupus erythematosus (4.6%) or family history of PE (3.1%). Of these, only 15 women (23.1%) were prescribed low-dose aspirin, at a mean gestational week of 13 weeks six days. Of the total 114 women with a recognised risk factor in this cohort, 38 (33.3%) developed PE, 26 of whom were not prescribed aspirin. Three women (3.2%) in the group who were not prescribed aspirin developed early-onset severe PE (including one with HELLP). Six (28.6%) women who were prescribed aspirin developed early onset or severe PE, including three with HELLP.

Obstetric and neonatal outcomes

The mode of delivery for women from each group is shown in Figure 2. The number of women who had delivery for suspected compromise were: CH untreated (one; 5.9%), GH untreated (11; 4.6%), GH treated (two; 6.9%); and PE (two; 1.0%). Neonatal outcomes are summarised in Table 4.

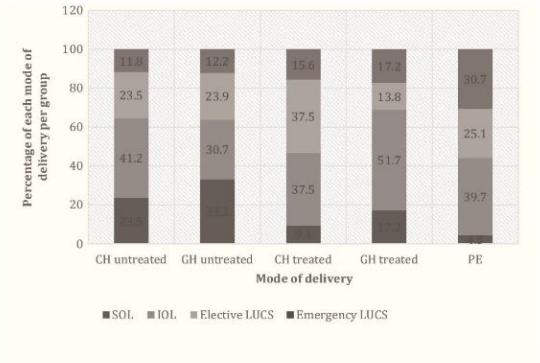


FIGURE 2 Mode of delivery per group. Emergency LUCS, emergency caesarean; Elective LUCS, elective caesarean; IOL, induction of labour; SOL, spontaneous onset of labour.

Eighty-six women developed severe hypertension during their pregnancy: three (17.6%) CH untreated, 13 (5.4%) GH untreated, six (18.8%) CH treated, nine (31.0%) GH treated and 55 (27%) PE; of these, 65 progressed from mild-moderate hypertension to severe hypertension, 37 (56.9%) of whom were prescribed antihypertensive medication. One hundred and thirty-five (56.5%) women with untreated GH progressed to mild or severe PE or HELLP, compared to 49/78 (62.8%) of those prescribed an antihypertensive. Fifteen women (23.4%) with CH progressed to at least mild PE. There were two incidences of placental abruption in women who had severe PE, neither of whom were prescribed antihypertensive medication or aspirin. The mean gestational age at delivery for the total cohort was 38 weeks and one day (± 16 days) (Table 4).

There were two perinatal deaths. One case presented with fetal death *in utero* at 38 weeks and was later diagnosed with severe hypertension; the second occurred in the context of severe mid-trimester FGR and PE. The most frequent perinatal complication across the groups was FGR, indicated in Table 4.

DISCUSSION

Our study shows that clinical guidelines for women with hypertension are largely being followed, although there is potential for improvement in compliance with prescription of aspirin prophylaxis for the prevention of PE. This study also reports a low incidence of major adverse events, suggesting that clinician compliance with institutional and SOMANZ clinical guidelines is safe and effective. In this cohort, it was common for near term hypertension to be managed expectantly, contrasting data from the United States in the same timespan.[8] Less than one-quarter of 'HYPITAT eligible' patients were delivered at 37 weeks, yet we observed a lower rate of adverse maternal outcome in this group than would have been predicted by HYPITAT. In part, this is because expectant management for this cohort was not prescribed by the HYPITAT endpoints, that is, delivery at 41 weeks unless severe hypertension or proteinuria, eclampsia, HELLP syndrome, fetal distress or prelabour rupture of membranes supervenes. The SOMANZ guidelines advise considering delivery after 37 weeks, particularly if maternal or fetal complications have developed. Many patients in this study were therefore managed expectantly until after 37 but prior to 41 weeks, which may explain some of the observed differences in major adverse events in this cohort compared to HYPITAT. This suggests that clinicians are actively weighing up the potential maternal benefit of immediate delivery versus neonatal harm, including the long-term consequences of late preterm and early term birth, which are being increasingly recognised. HYPITAT-II has specifically addressed this: among women with mild GH or PE between 34–37 weeks, expectant management was associated with a small and non-significant increase in maternal adverse outcomes, but a significant reduction in neonatal respiratory distress, leading the authors to conclude that delivery should be deferred until 37 weeks, unless maternal deterioration supervenes.[3]

Blood pressure levels for diagnosis of hypertension, thresholds at which anti-hypertensive medication were initiated, and choice of antihypertensive were consistent with both the 2008

TABLE 3 Thresholds for diagnosis of hypertension and initiation of anti-hypertensive treatment

	GH untreated (*n* = 239)	GH treated (*n* = 29)	CH treated (*n* = 32; 15 initiated treatment during pregnancy)	PE (*n* = 199) 64 treated: GH (*n* = 49), CH (*n* = 15)
Systolic BP at the time of diagnosis, mean ± SD	140 ± 10 mmHg	151 ± 13 mmHg	Pre-pregnancy	146 ± 13 mmHg
Diastolic BP at the time of diagnosis, mean ± SD	89 ± 8 mmHg	95 ± 9 mmHg	Pre-pregnancy	92 ± 9 mmHg
Gestational week at which the women were diagnosed with hypertension, mean ± SD	35[2] weeks ± 31 days	32[3] weeks ± 34 days	Pre-pregnancy	33[1] weeks ± 44 days
Systolic BP at which medication was initiated, median (IQR)	N/A	153 mmHg (140–156)	156 mmHg (135–215)	153 mmHg (130–185)
Diastolic BP at which medication was initiated, median (IQR)	N/A	94 mmHg (60–122)	97 mmHg (80–130)	99 mmHg (80–160)

BP, blood pressure; CH, chronic hypertension; GH, gestational hypertension; IQR, interquartile range; PE, pre-eclamspia

TABLE 4 Neonatal outcomes (n = 524)

Neonatal outcomes	CH untreated (n = 17)	CH treated (n = 32)	GH untreated (n = 238)	GH treated (n = 30)	Pre-eclampsia (n = 207)
Gestational age at delivery, mean ± SD	38 weeks ± 8 days**	37 weeks ± 22 days**,***[1]	39 weeks ± 13 days***,***[1]	38 weeks ± 13 days**	36 weeks ± 29 days**
Customised birth weight centile, mean ± SD (range)†	63.1 ± 28.5 (27.8–99.3)*	29.9 ± 23.5 (0.3–78.0)*	48.6 ± 31.1 (0.1–100.0)*[1]	43.6 ± 30.8 (0.4–95.4)	37.9 ± 32.1 (0.0–100)*[1]
Fetal growth restriction, n (%)†	0 (0)	7 (21.9)	30 (12.6)	5 (16.7)	45 (21.7)
APGAR at one min, mean ± SD (range)	9 ± 1 (3–10)	7 ± 2 (0–9)	8 ± 2 (1–10)**	8 ± 2 (2–10)	7 ± 2 (0–10)**
APGAR at five min, mean ± SD (range)	9 ± 1 (7–10)	9 ± 1 (6–10)	9 ± 1 (0–10)*	9 ± 1 (6–10)	9 ± 1 (0–10)*
NICU admission, n (%)	1 (5.9)	6 (18.8)	12 (5.0)	2 (6.7)	59 (28.5)
SCN admission, n (%)	1 (5.9)	0 (0)	17 (7.1)	3 (10.0)	38 (18.4)

CH, chronic hypertension; GH, gestational hypertension; NICU, neonatel intensive care unit; PE, pre-eclamspia; SCN, special care nursery
[1] P = 0.02; *,***[1] P < 0.01. [1,2]groups which are being compared. †Some missing data.

and 2014 SOMANZ guidelines.[3,4] The majority of women who had CH were initiated on antihypertensive medication prior to pregnancy by their general practitioner, which continued throughout pregnancy. Choice of anti-hypertensive medication across the cohort was appropriate, the majority being initiated on labetalol during pregnancy. The higher proportion of methyldopa prescriptions in the CH treated group suggests that general practitioners remain more familiar with methyldopa than labetalol as a first line agent, despite the demonstrable safety, better tolerance and efficacy of the latter in preventing progression to severe hypertension.[14] A Canadian study of prescribing for hypertension during pregnancy by general practitioners reported similar prescribing patterns.[15]

The appropriate threshold for initiating antihypertensive therapy remains unclear. There is an undisputed need for treatment of severe hypertension (BP ≥ 160/110 mmHg).[4] The Centre for Maternal and Child Enquiries in the UK recommends including the treatment of a systolic BP of ≥150 mmHg as one of its top ten recommendations.[16] A recent systematic review was inconclusive regarding the benefits of treatment of mild-moderate hypertension during pregnancy, confirming that treatment of mild-moderate hypertension does not influence progression to PE.[14] The recently published Control of Hypertension In Pregnancy Study (CHIPS)[17] found no significant differences in the risk of pregnancy loss, high-level neonatal care or overall maternal complications between less-tight (target diastolic BP 100 mmHg) versus tight (target diastolic BP 85 mmHg) control of hypertension. However, there was an observed higher incidence of severe hypertension in the less-tight group. While this study was expected to inform the debate regarding treatment of mild-moderate hypertension, it seems likely that treatment will continue to be dictated by local clinical practice and individual prescribing patterns.

While PE was more common in the GH treated group, PE also complicated 36% of cases whose hypertension was not severe enough to require treatment, confirming that these women needed to remain under close surveillance. In this cohort, all women who developed hypertension were referred to the Pregnancy Assessment Day Centre after initial diagnosis, where outpatient surveillance with serial assessments of maternal and fetal well-being are undertaken. Furthermore, the incidence of severe hypertension was similar between the treated and untreated groups, highlighting that all women with hypertension in pregnancy require continued close surveillance to ensure that severe hypertension is recognised and managed appropriately. With regard to perinatal outcomes, FGR was more common among women with treated CH than other hypertensive groups, and similar to the rate observed among women with PE. These findings are consistent with other reports,[18] and likely reflect that women requiring treatment for CH have more severe disease. They are also more likely to have underlying conditions such as renal or connective tissue disease, themselves important contributors to placental insufficiency and FGR. Nevertheless, some of the observed differences may also be due to chance, given the small numbers and increased maternal age and smoking rates, in this group.

Although low-dose aspirin (initiated at or before 16 weeks gestation) has been found to reduce risk of PE[19,20] and is widely recommended in international guidelines, many high-risk women in this cohort were not prescribed aspirin or calcium, despite the majority being seen initially prior to 16 weeks gestation. In particular, the prescription of aspirin in the CH groups was suboptimal, and the number of women who progressed to PE consistent with historical cohorts.[18] The relative risk associated with aspirin administration and prevention of PE has been reported between 0.47[19] and 0.76.[20] Based on this, an estimated 12[19] to 19[20] cases of PE may have been averted in our cohort had this recommendation been followed, although this may overestimate the number of excess cases given that aspirin has greater efficacy in reducing the burden of early onset, compared to late onset, disease.[21] Our study design was unable to answer the important question as to which women with risk factors may have received aspirin and subsequently did not develop PE.

To the best of our knowledge, prescribing patterns in pregnant women with hypertension in Australia have not been reported before. Although this was a single centre study, it was conducted

at a large tertiary care hospital and data were collected over a 12-month period by a single researcher. The study relied solely on ICD coding for identification of cases. The small proportion of women who were prescribed medication limited our ability to conduct further analysis of that data.

In conclusion, while hypertension management guidelines were generally well followed, the opportunity for primary prevention of PE or FGR in high-risk women with aspirin prophylaxis was frequently overlooked. Broader education beyond clinical practice guidelines of all maternity care providers is necessary to improve aspirin coverage in these women. In this cohort alone 12–19 excess PE cases may have been averted. Despite the findings of HYPITAT, uptake of the key trial recommendation to encourage delivery at or beyond 37 weeks in this cohort was low; however, we observed very low rates of adverse maternal outcome in women managed expectantly, suggesting that clinicians appropriately weigh up the likely maternal risk compared to infant benefits of deferred delivery in each case, a key recommendation of HYPITAT-II.

ACKNOWLEDGEMENTS

We would like to thank Denise van den Bosch for assistance with data entry and the Health Information Services team at the Mercy Hospital for Women for retrieving the medical records. We acknowledge Andre Francis and Professor Jason Gardosi for help with the customised centiles.

REFERENCES

1. Roberts CL, Algert CS, Morris JM *et al*. Hypertensive disorders in pregnancy: a population-based study. *Med J Aust* 2005; **182**: 332–5.
2. Pouta A, Hartikainen AL, Sovio U *et al*. Manifestations of metabolic syndrome after hypertensive pregnancy. *Hypertension* 2004; **43**: 825–31.
3. Lowe SA, Brown MA, Dekker GA *et al*. Guidelines for the management of hypertensive disorders of pregnancy 2008. *Aust N Z J Obstet Gynaecol* 2009; **49**: 242–6.
4. Lowe SA, Bowyer L, Lust K *et al*. The SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. *Aust N Z J Obstet Gynaecol* 2015; **55**: 11–16.
5. Koopmans CM, Bijlenga D, Groen H *et al*. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009; **374**: 979–88.
6. World Health Organisation. ICD. Chapter XV Pregnancy, childbirth and the puerperium (O00-O99) Oedema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium (O10-O16).
7. Mongelli M, Figueras F, Francis A, Gardosi J. A customized birthweight centile calculator developed for an Australian population. *Aust N Z J Obstet Gynaecol* 2007; **47**: 128–31.
8. Pauli JM, Lauring JR, Stetter CM *et al*. Management of gestational hypertension - the impact of HYPITAT. *J Perinat Med* 2013; **41**: 415–20.
9. Crump C, Sundquist K, Winkleby MA, Sundquist J. Early-term birth (37–38 weeks) and mortality in young adulthood. *Epidemiology* 2013; **24**: 270–6.
10. Harijan P, Boyle EM. Health outcomes in infancy and childhood of moderate and late preterm infants. *Semin Fetal Neonatal Med* 2012; **17**: 159–62.
11. Lipkind HS, Slopen ME, Pfeiffer MR, McVeigh KH. School-age outcomes of late preterm infants in New York City. *Am J Obstet Gynecol* 2012; **206**: 222 e1–6.
12. McGowan JE, Alderdice FA, Holmes VA, Johnston L. Early childhood development of late-preterm infants: a systematic review. *Pediatrics* 2011; **127**: 1111–24.
13. Broekhuijsen K, van Baaren GJ, van Pampus MG *et al*. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial. *Lancet* 2015; **385**: 2492–501.
14. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2014; **2**: CD002252.
15. Xie R-h, Guo Y, Krewski D *et al*. Trends in using beta-blockers and methyldopa for hypertensive disorders during pregnancy in a Canadian population. *Eur J Obstet Gynecol Reprod Biol* 2013; **171**: 281–5.
16. Cantwell R, Clutton-Brock T, Cooper G *et al*. Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; **118**(Suppl 1): 1–203.
17. Magee LA, von Dadelszen P, Rey E *et al*. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med* 2015; **372**: 407–17.
18. Sibai BM. Chronic hypertension in pregnancy. *Obstet Gynecol* 2002; **100**: 369–77.
19. Bujold E, Roberge S, Lacasse Y *et al*. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010; **116**: 402–14.
20. Henderson JT, Whitlock EP, O'Connor E *et al*. Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2014; **160**: 695–703.
21. Roberge S, Villa P, Nicolaides K *et al*. Early admisitration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. *Fetal Diagn Ther* 2012; **31**: 141–6.

3.3 Discussion and Summary

The retrospective cohort study provided an insight into the management of HDP. The overlooking of low-dose aspirin for the primary prevention of fetal growth restriction and PE was evident. This drew attention to the fact that, although low-dose aspirin is a readily accessible intervention in the prevention of PE when initiated at an appropriate time point in the pregnancy (prior to 16 weeks), only a minority of pregnant women at high risk of developing PE were started at an appropriate time point. More recently there has been some debate pertaining to primary PE prevention, which entails the administration of aspirin to women who has not had previous PE or current chronic hypertension. Atallah et al reviewed the evidence-based indications for primary and secondary prevention of pre-eclampsia (246). They reported that despite some controversies in the use of aspirin it is clear that low doses of aspirin are effective in secondary prevention of pre-eclampsia in high-risk patients, mainly those with a history of preeclampsia. Indications for aspirin in primary prevention are a matter of debate, but recent publications suggest a strategy based on first-trimester screening of pre-eclampsia (with clinical parameters, biomarkers and uterine Doppler measurements) and aspirin administration to high-risk patients. The usefulness of this strategy is still under evaluation and more data are needed before its wider implementation in clinical practice. (246)

Similarly, prescribing patterns of antihypertensive medication during pregnancy had not been previously reported. This cohort showed that Australian guidelines regarding prescription of antihypertensive medications during pregnancy are generally well followed, with the majority of women receiving a prescription for methyldopa or labetalol.

At the time of data collection for this phase, the results of the 'Induction of labour versus expectant monitoring for gestational hypertension or mild PE after 36 weeks gestation' trial (HYPITAT) had only been recently published and the recommendation for early induction of labour had not yet been updated in the SOMANZ guidelines. Despite this, the retrospective cohort study showed that clinicians were mindful of the balance between maternal and fetal risks of early induced delivery and provided an early indication from the field that HYPITAT was due to make a positive impact on the risk versus benefit balance. This was predictable, as HYPITAT was a randomised controlled trial with a sizeable participant number with sufficient statistical power. The later SOMANZ 2015 guidelines included the HYPITAT recommendation.

The retrospective cohort provided clearer understanding of the number of women with hypertensive disorders of pregnancy who are prescribed an antihypertensive during pregnancy. This helped to inform the number of participants required for Phase 2 of the project, as described in **Chapters 4, 5, 6 and 7**. It was not possible to ascertain patients' perspectives and behaviours regarding medication adherence and clinical management through the retrospective cohort, so a

prospective cohort study, encompassing a survey which included a nonadherence scale as well as in-depth interviews was required to achieve the aims and objectives of the thesis.
Furthermore, although the retrospective cohort did not yield substantial results with regard to adherence to antihypertensives during pregnancy, there was mention of nonadherence in about a dozen medical files, which indicated that nonadherence to antihypertensives was negatively impacting on the women's condition and that optimising adherence may have been a priority for some clinicians. This led to the survey reporting the quantitative adherence to antihypertensive medication to be presented as the next sub-phase (**Chapter 4**).

CHAPTER 4

ADHERENCE TO ANTIHYPERTENSIVE MEDICATION IN PREGNANCY SURVEY

4.1 Introduction

An observation reported in **Chapter 3** indicated that nonadherence to antihypertensives during pregnancy suggested a possible problem in this population.

As there were no published works regarding adherence to antihypertensives during pregnancy at the time, there was a need to undertake research to estimate adherence or lack thereof and to identify factors influencing adherence or lack thereof in this population. Furthermore, gaining knowledge of adherence by this population to antihypertensive medication contributed towards gaining an understanding of medication use by pregnant women with hypertensive disorders of pregnancy, a thesis objective that is shared with **Chapter 5**.

This chapter reports research about adherence to antihypertensive medication during pregnancy conducted in pregnant women diagnosed with HDP and prescribed an antihypertensive medication at two tertiary maternity hospitals in Melbourne. The aim of this study was to assess their adherence to antihypertensive medication and to identify the factors associated with adherence or lack thereof.

A cross-sectional survey, which incorporated a nonadherence scale, was conducted with 100 pregnant women with a diagnosis of HDP and prescribed an antihypertensive. Self-reported reasons for adherence and lack thereof were obtained from the nonadherence scale and were supplemented by quotes from in-depth interviews (to be discussed further in **Chapters 5 and 6**) to provide a deeper understanding of the motivations for adherence or lack thereof.

This manuscript is published in **Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health** and is reproduced below.

Appendices relevant to this chapter are appendix 5, 6, 7, 8, 9, 12, 13, 14 and 15.

4.2 Published Manuscript: Helou A, Stewart K, George J. Adherence to anti-hypertensive medication in pregnancy. Pregnancy Hypertens. 2021;25:230-24.

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 25 (2021) 230–234

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

Adherence to anti-hypertensive medication in pregnancy

Amyna Helou, Kay Stewart, Johnson George *

Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Victoria, Australia

ARTICLE INFO

Keywords:
Adherence
Anti-hypertensives
Pregnancy
Gestational hypertension
Chronic hypertension

ABSTRACT

Objectives: To assess adherence to anti-hypertensive medication by pregnant women and to identify the factors associated with adherence or lack thereof.
Study Design: Observational study in 100 pregnant women with either chronic hypertension or gestational hypertension who were being treated with at least one anti-hypertensive medication and attending antenatal clinics at one of two maternity hospitals.
In-depth interviews were conducted with a subset of 27 women from the same group. Quotes from interview transcripts were used to illustrate the quantitative results.
Main Outcome Measures: BP control, self-reported adherence, complexity of medication regimen.
Results: Participants (mean age 33 [±4.9] years; mean gestation 29 (±7) weeks) had a median blood pressure (BP) of 130/80 mmHg (IQR: 16/15). Sixty-five women had chronic hypertension, of whom 13 were diagnosed during pregnancy, before 20 weeks gestation. Thirty-five women had gestational hypertension. Ninety-two per cent of participants had sub-optimal adherence. There were no significant differences in adherence scores between participants with chronic hypertension and their counterparts. The main contributors to sub-optimal adherence were intentionally putting up with medical problems before taking any action, confusion about the medication, and making changes to the recommended medication regimen to suit lifestyle.
Conclusions: Nine out of ten pregnant women using anti-hypertensives self-reported some degree of suboptimal adherence, intentionally and/or unintentionally. Health professionals, including pharmacists, general practitioners and obstetricians, have a role in promoting optimal medication adherence.

1. Introduction

Nonadherence to medication can contribute significantly to treatment failure and unnecessary over-prescribing [1]. Adverse effects, complex dosage schedules and lack of understanding of the condition are some of the factors associated with poor adherence to anti-hypertensive medications in the general population [2]. Nonadherence to anti-hypertensive medications in the general population has been classified as intentional and/or unintentional [3]. Intentional non-adherence involves a patient altering their dosage regimen to suit their own needs [4]. This is associated with their beliefs about the medication and involves a 'decision balance' [4]. A recent study investigating women's perceptions of medication use during pregnancy and breast-feeding found that women perceived medication use during early or late pregnancy as 'probably harmful' or 'harmful' [5]. A study examining adherence of pregnant women from 18 countries found that many had poor adherence to their chronic pharmacotherapy regimens during pregnancy [6]. Studies of pregnant women with specific pre-pregnancy disease states, namely HIV-AIDS [7], Crohn's disease [8], ulcerative colitis [9] and asthma [10] have reported fear of negative impacts of the medication on the fetus as the main reason for nonadherence [7–10]. Studies of adherence to medications, specifically for pregnancy-induced conditions, have been scant. A study of adherence to low-dose aspirin in high-risk pregnancies found nonadherence to vary from 21.4% to 46.3% [11]. Good adherence to treatment for pregnancy-induced conditions such as gestational hypertension is important to optimise health outcomes for the mother and the fetus [12].

Direct and indirect measures of adherence are available. Objective clinical measurements, such as drug concentration in the blood, or surrogate measures, such as BP, can be used to gauge adherence [13]; however, their utility during pregnancy is limited because many physiological factors impact on drug levels and the progression of hypertension during pregnancy [14]. Moreover, the duration of medication taking during hypertensive disorders of pregnancy is often limited to a

* Corresponding author.
E-mail address: Johnson.George@monash.edu (J. George).

https://doi.org/10.1016/j.preghy.2021.06.002
Received 6 September 2020; Received in revised form 27 May 2021; Accepted 2 June 2021
Available online 8 June 2021

short period from the time of diagnosis until delivery [15].

Self-reporting may be overestimated, but offers a simple method for quantifying adherence [16]. It has been recommended as the most suitable measure in routine clinical practice [16]. Several measures of self-reported adherence are available [17]. These include scales such as the Morisky scale [18] and the Tool for Adherence and Behaviour Screening (TABS) [19]. Other forms of self-report include personal diaries and qualitative interviews.

The objective of this study was to assess adherence to anti-hypertensive medication by pregnant women and to identify the factors associated with adherence or lack thereof.

2. Methods

Pregnant women with a documented history of hypertension during their current pregnancy were prospectively recruited through two Australian maternity hospitals over a 10-month period. The women were identified by screening outpatient medical records that were prepared for the antenatal outpatient clinic the following day. Diagnostic criteria for chronic hypertension (CH), gestational hypertension (GH) and preeclampsia (PE) were based on the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guidelines for the management of hypertensive disorders during pregnancy 2008 [16]. Pregnant women with either CH or GH who were being treated using at least one anti-hypertensive medication were included in the study. Women under the age of 18 years, non-English speaking or those who did not wish to be contacted for research, were excluded. Recruitment continued until the desired sample size of 100 was reached.

A 23-item questionnaire (Supplementary material, Appendix S1), which incorporated the nonadherence sub-scale of the TABS [9], was administered to all participants at the time of their scheduled clinic visit. The 'nonadherence' sub-scale of the TABS is useful for the quantification of nonadherent behaviour and has been used in both general and pregnant populations [11,17].

Questions on adherence were related to the patient's current medication regimen, including their anti-hypertensive and any other prescription or over-the-counter medications. Participants were also asked to self-report their perceived BP control. Demographic, clinical and obstetric data were collected from the clinic records.

For each of the four items on the TABS 'nonadherence' subscale, a response 'Always' gave a score of 5, whilst a response 'Never' gave a score of 1. A total 'nonadherence' score of 4 suggested perfect self-reported adherence whilst a score 5 or above suggested suboptimal adherence. The Medication Regimen Complexity Index (MRCI) was used to calculate the complexity of the participants' medication regimens [20]. The index comprises three sections: dosage form, dosage frequency and additional instructions. A score above 10 was regarded a simple regimen while a score of 10 and above indicated a complex regimen. The MRCI scores of 10% of the medication profiles were independently calculated by another author (JG) to establish inter-rater reliability. MRCI scores had high inter-rater reliability (inter-class correlation coefficient [ICC] = 0.999). Each section of the MRCI was analysed in relation to self-reported adherence.

Data were entered into SPSS (version 25.0, IBM, New York, NY, USA) and analysed using descriptive statistics (Mean ± standard deviation [SD] or Median ± interquartile range [IQR] or number [%]).

Factors associated with nonadherence were identified in univariable analyses using Student's *t*-test, Chi-square, and Mann-Whitney *U* test, followed by linear regression. A p-value <0.05 was regarded as statistically significant.

In-depth interviews were conducted with a subset of the participants (full results to be reported elsewhere). Quotes from these interviews have been used to illustrate some of the findings.

Participants gave informed consent and ethics approvals were obtained from the Human Research Ethics Committees of each of the participating hospitals and Monash University.

3. Results

Data were collected from a total of 98 participants. One participant did not complete the questionnaire as she had a fetal death *in utero* prior to the scheduled meeting with the researcher; the other completed the questionnaire at home but had an emergency caesarean following placental abruption soon after and failed to return her response. Completion of the questionnaire occurred in the second or third trimester, at a mean of 29 (±7) weeks gestation.

The demographic and clinical characteristics of the participants are shown in Table 1. Two in five women reported at least one co-morbid condition. The most common co-morbid conditions were kidney disorders and gestational diabetes. Other reported conditions included ulcerative colitis, polycystic ovarian syndrome and asthma.

Table 2 describes the nature of the self-reported BP and the prescribed anti-hypertensive medication. The majority of participants (94.9%) were prescribed either labetalol and/or methyldopa.

Table 3 details the responses to each item from the TABS nonadherence scale [9]. The range for the nonadherence scores was 17–4, with 17 indicating poorest adherence. The median (IQR) nonadherence score was 6. Only eight participants had a score of 4, indicating perfect adherence.

There were no significant differences in adherence between those who self-reported completely/well controlled BP and those who self-reported somewhat/poorly/not at all controlled BP.

Univariable analysis showed no significant associations between suboptimal adherence and any of the characteristics investigated (Table 4). In addition, no differences in adherence rates were found between the two study sites.

Table 5 describes the incidence of adverse outcomes in pregnancy amongst the perfect and suboptimal adherence groups. No efforts were made to draw links of causation and effect due to the small sample size and multiple factors that may have impacted the outcomes in women affected by hypertensive disorders of pregnancy.

The MRCI gave insight into the complexity of the overall medication regimens of the participants.

Seventeen (17.3%) participants had a total score of more than 1 for

Table 1
Self-reported baseline characteristics of participants (N = 98).

Demographics	N (%)
Age (years) mean (±SD)	33 (±4.9)
Highest educational level	
Secondary School	11 (11.2)
Technical and Further Education	30 (30.6)
University	59 (60.2)
Concession card holder	17 (17.3)
Born in Australia	56 (57.1)
Spoke at least one language other than English	35 (35.7)
Clinical	**N (%)**
Gestational week at completion of questionnaire mean (±SD)	29(±7.5)
Parity	
Nulliparous	48 (49)
Multiparous	50 (51)
Smoking status	
Current smoker	2 (2)
Ex-smoker	39 (39.8)
Never smoker	57 (58.2)
Co-morbidity	
Kidney disorders	7 (7.1)
Hypothyroidism	4 (4.1)
Type 2 diabetes	4 (4.1)
Gestational diabetes	5 (5.1)
Depression/anxiety	4 (4.1)

Table 2
Summary of BP and anti-hypertensive medication (N = 98).

Nature of BP	N (%)
Blood pressure on day of survey completion median (range)	
Systolic BP	130 (100–160)
Diastolic BP	80 (60–100)
Type of hypertension	
Chronic Hypertension	64 (65.3)
Diagnosed during current pregnancy	13
Treatment initiated during current pregnancy	21
Gestational hypertension	34 (34.7)
Anti-hypertensive medication*	
Labetalol	52 (53.1)
Methyldopa	41 (41.8)
Nifedipine	6 (6.1)
Oxprenolol	2 (2.0)
Atenolol	2 (2.0)
Phenoxybenzamine	1 (1.0)
Prazosin	1 (1.0)
Perceived BP control	
Completely controlled	19 (19.4)
Well controlled	39 (39.8)
Somewhat controlled	31 (31.6)
Poorly controlled	3 (3.1)
Not at all controlled	3 (3.1)
Do not know	2 (2.0)

*Total >98 because some were prescribed multiple medications.

Table 3
Responses to questions on adherence and nonadherence (N = 98).

Question	Response n (%)				
	Always	Often	Sometimes	Rarely	Never
I have strict routines for using my medications	55 (56.1)	29 (29.7)	12 (12.2)	2 (2)	0 (0)
I ensure I have enough medications so that I do not run out	70 (71.4)	18 (18.4)	8 (8.2)	2 (2)	0 (0)
I strive to follow the instructions of my doctors	71 (72.4)	21 (21.4)	1 (1)	0 (0)	0 (0)
NONADHERENCE SCALE					
I get confused about my medications	0 (0)	0 (0)	11(11.2)	34 (34.7)	53 (54.1)
I make changes in the recommended medication management to suit my lifestyle	2 (2)	2 (2)	9 (9.2)	26 (26.6)	59 (60.2)
I vary my recommended medication management based on how I am feeling	0 (0)	1 (1)	8 (8.2)	25 (25.5)	64 (65.3)
I put up with my medical problems before taking any action	2 (2)	2 (2)	33 (33.7)	31 (31.6)	30 (30.6)

dosage form indicating that they were prescribed more than one dosage form. Of these, 15 (88.2%) participants self-reported suboptimal adherence. The remaining 81 (82.7%) participants had a total score of 1 for this section, indicating they were only using oral medications. Of these, 74 (91.4%) participants self-reported suboptimal adherence.

Nine participants were prescribed once daily regimens and all self-reported suboptimal adherence. Eighty (89.9%) of the remaining 89 participants self-reported suboptimal adherence. Thirty-two (32.7%) had scores ≤ 4, of whom 29 (90.6%) reported suboptimal adherence. Sixty-six (67.3%) had scores above 4, of whom 60 (90.9%) reported suboptimal adherence.

Twenty-one participants (21.4%) had no additional directions. Of these, 19 (90.5%) self-reported suboptimal adherence. Of the 77 participants who did have additional directions, 72 (93.5%) self- reported suboptimal adherence.

Table 4
Adherence and patient characteristics (N = 98).

Characteristic	Perfect adherence N = 8	Sub-optimal adherence N = 90	p-value
Age (years) Mean(±SD)	34 (3.9)	33 (5.0)	0.727
Gestational week at completion of questionnaire Mean (±SD)	29 (6)	29(7)	0.987
Highest educational level (N %)			
• Secondary	1 (12.5)	10 (11.1)	
• TAFE	2 (25)	25 (27.8)	
• University	5 (62.5)	55 (61.1)	0.982
Country of birth (N%)			
Australia	5 (62.5)	51 (56.7)	0.749

Table 5
Adherence and outcomes (N = 98).

Outcome	Perfect adherence N = 8	Suboptimal adherence N = 90
Systolic BP on survey completion in mmHg, mean(±SD)	131 (7.4)	131 (12.6)
Diastolic BP on survey completion in mmHg, mean(±SD)	78 (8.5)	82 (10.6)
Incidence of severe hypertension* throughout pregnancy, N(%)	2 (25.0)	19 (21.1)
Preterm delivery, ** N(%)	1 (12.5)	21 (23.3)
Emergency delivery, N(%)	5 (62.5)	37 (41.1)

* ≥170 and/or ≥110 mmHg.
**Before 37 weeks gestation.
BP – blood pressure.

The eight women who self-reported perfect adherence had a median age of 34 years (range 29–42 years). Six (75%) of these women were multiparous while two (25%) were primiparous; two (25%) were in their second trimester and six (75%) were in their third trimester at the time of survey completion. Six (75%) had CH and two (25%) had GH with a median systolic BP of 128 mmHg (range 125–140) and median diastolic BP of 80 mmHg (range 60–85). Four (50%) women were prescribed methyldopa and four (50%) were prescribed labetalol. One was also prescribed nifedipine. The median number of medications was four (range 2–7) and the median number of dosage forms was one (range 1–2).

No significant associations between the complexity of the regimens and self-reported nonadherence were observed.

Nine out of ten pregnant women treated using anti-hypertensives reported some degree of nonadherence, intentionally to suit their lifestyle or unintentionally due to forgetting or being confused about their medication.

The in-depth interviews provided some additional insight into self-reported nonadherence.

Women who described putting up with medical problems before taking any action often preferred to remain oblivious to the risks of not taking their anti-hypertensive, either out of fear or feeling overwhelmed with information:

> *"I have sort of avoided asking because I have been a bit scared* [nervous laughter]." *(#21, 35 years, 1st pregnancy, second trimester, chronic hypertension)*
> *"It was very overwhelming. I didn't know how to take it at first." (#8, 36 years, 2nd pregnancy, third trimester, chronic hypertension)*

Others would forget to take their anti-hypertensive as prescribed because they had not incorporated it into their routine. Some commented that they did not notice any difference in how they felt when

they unintentionally forgot to take a dose:

> *"I just used to take it, but a lot of times I never used to take it because I used to forget…because I wasn't used to it…" (#22, 37 years, 3rd pregnancy, third trimester, chronic hypertension)*
> *"A couple of times I forgot to take it and nothing happened to me." (#9, 30 years, 1st pregnancy, second trimester, chronic hypertension)*

Some women were uncertain about the need for the anti-hypertensive, either as a result of a lack of symptoms or conflicting advice from different clinicians about when to initiate anti-hypertensive treatment:

> *"I was a bit…confused…at the beginning of the pregnancy…because I saw that my blood pressure…wasn't that high. So I thought 'Why should I take the* [medicine]*? Should I take it or not?'" (#11, 33 years, 2nd pregnancy, second trimester, chronic hyertension)*
> *"I mentioned to him* [Physician] *that I'd had to start the blood pressure tablets…he said 'I don't understand why they* [treating obstetrician] *got you to start the tablets, not according to your readings' …*[so] *I was really unclear and not sure…I just thought 'What have I done? I've been putting this medication in my body'." (#24, 35 years, 1st pregnancy, third trimester, chronic hypertension diagnosed during pregnancy before 20 weeks gestation)*

Others felt that taking their anti-hypertensive as prescribed would interfere with their lifestyle and reported being preoccupied with daily routines as a reason for their suboptimal adherence:

> *"I get busy…like this morning, I normally take them with breakfast, but then I took my daughter to the childcare and I'm like 'Oh I haven't taken any of my meds… I took them when I got home." (#74, 36 years, 2nd pregnancy, third trimester, chronic hypertension)*
> *"You've got to remember I was working two jobs too so I was busy…I'm a busy person, four kids, too many things to do…" (#90, 35 years, 7th pregnancy, third trimester, chronic hypertension)*

4. Discussion

Self-reported nonadherence in this population was higher than the reported rate of 25% partial or total nonadherence to anti-hypertensive medication in the general adult population [21] and in other high risk pregnancy populations (21.4–46.3%) [11]. It seems logical to assume that pregnant women who had hypertension would demonstrate good adherence to medications due to the risk of pregnancy complications and potential risks to the fetus [15]. This, however, was not the case. It may be that pregnant women are more worried about risk to the fetus from taking medication during pregnancy, than the risks from high BP, as reported in pregnant women with asthma [10].

Demographic and clinical characteristics were not associated with medication use. This is in contrast to studies in the general population that suggest that age, ethnicity and education status may be important determinants of adherence to medications [1], but consistent with other medication adherence studies involving high risk pregnancies [11]. One study quantified adherence to anti-hypertensive medication for chronic hypertension during pregnancy by measuring urinary metabolites of labetalol and nifedipine and reported an adherence rate of 88% [22]. However, this was a randomised controlled trial comparing two different anti-hypertensive agents with ongoing monitoring of adherence and support [22,23]. On the other hand, we assessed adherence to anti-hypertensive medications in 'real life' and researchers not involved in the clinical care of participants collected data, hence reflecting 'in practice' adherence.

The lack of association between self-reported nonadherence and regimen complexity is in contrast to a recent meta-analysis which found an association between higher MRCI scores and nonadherence [24].

One-third of participants reported that they sometimes put up with medical problems before taking any action. A preference to remain oblivious to the risks of uncontrolled high blood pressure was evident in some of the women who participated in the in-depth interviews. This contributed to them putting up with medical problems without paying attention to taking the anti-hypertensive. Studies have also shown that pregnant women may avoid treatment of their medical problems to avoid taking a medication that may be harmful for the fetus [25]. A study of pregnancy-related calls from an Australian medicines information line found that pregnant women were concerned about safety of medications and that a substantial number of women overestimated the potential risk [26].

Similarly, medical treatment avoidance has been reported in various disease states [27]. Further study of this population is warranted to elucidate specific factors related to this behaviour.

Confusion about the medication was another self-reported reason for suboptimal adherence. Confusion was evident when the anti-hypertensive medication was prescribed when BP was stable and when there was a difference in opinion between clinicians regarding the initiation of the anti-hypertensive. The latter is a long-standing controversy between treating doctors regarding the initiation of treatment of mild-moderate hypertension (140–160/90–100 mm Hg) [15]. The Control of Hypertension In Pregnancy Study, a large international, multi-centre trial [18], explored this controversy but did not reach a conclusion. The decision to treat remains at the discretion of the treating obstetrician/physician and is not referenced to a guideline such as SOMANZ [15]. Similarly, some women reported that if they forget to take the anti-hypertensive as prescribed, they would not notice any difference in symptoms. The absence of symptoms of hypertension is well known and has been shown to contribute to confusion [28]. Pregnant women should be encouraged to ask questions of their prescribing physician or community pharmacist about their medications, especially regarding any concerns about safety.

Making changes to the recommended medication management to suit their lifestyle or according to how they are feeling, a form of intentional nonadherence, was also observed. It is important to note that 56% of participants had their treatment initiated during pregnancy. This may influence their ability to fit the new medication into their daily routine. Moreover, some women reported via the in- depth interviews that their current daily routines and commitments hindered them from taking their anti-hypertensive as prescribed would sometimes opt to miss the doses. Pharmacists can advise pregnant women on the best way to incorporate the new medication into their lifestyle.

To the best of our knowledge, this was the first study to assess adherence of pregnant women to anti-hypertensive medication during pregnancy. The triangulation of quotes from in-depth interviews in the same population enriched the quantitative results. Pregnant women from two major maternity hospitals in Victoria, including the largest public maternity hospital in Australia, participated in the study. Participants were from a variety of social and cultural backgrounds, reflective of the Australian population. Although self-report is prone to recall bias [17], participants answered the questions on the non-adherence scale in relation to their current pregnancy, the short time-frame thus minimising recall bias. Self-reporting of adherence can also result in overestimation of adherence [17]; however, the proportion of participants who self-reported suboptimal adherence was high, suggesting there was minimal overestimation of adherence. Women with poor English skills were excluded from the study, therefore, caution should be taken in the extrapolation our results to women from non-English speaking backgrounds. The sample size was such that the proportion of women reporting optimal adherence was too small to allow statistical identification of differences between the groups.

5. Conclusion

Suboptimal adherence was common in pregnant women treated using anti-hypertensives. Subtype of hypertension, maternal age and

medication regimen complexity did not contribute to nonadherence. Confusion about the need for medication, forgetting the dose and putting up with medical problems before taking any action did contribute to nonadherence. Health professionals including pharmacists, general practitioners and obstetricians have a role in promoting optimal adherence. This may help in improving patient outcomes and prevent complications. Further research needs to be conducted to evaluate the effect of behavioural and educational interventions on medication adherence and health outcomes.

6. Contribution to authorship

All authors contributed to the conception and design of the study. Patient recruitment, survey administration and in-depth interviews were undertaken by AH. Data analyses and interpretation were performed by all authors. All tables were generated by AH. The manuscript was written by AH and critically reviewed by all authors. All authors read and approved the final manuscript.

7. Details of ethics approval

This study received ethics approval from the Mercy Health Human Research Ethics Committee Heidelberg-Melbourne (R12/62) 08/01/2013, The Royal Women's Hospital Research and Human Research Ethics Committee Parkville-Melbourne (R13/18) 12/07/2013 and Monash University Human Research Ethics Committee Clayton-Melbourne (CF13/117) 18/01/2013.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Professor Susan Walker for comments on an earlier draft of this manuscript. We would also like to thank the staff at both the Mercy Hospital for Women and the Royal Women's Hospital for their help with this study. We would also like to thank all the women who participated in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2021.06.002.

References

[1] Sabate E. (Ed.) Adherence to long-term therapies: Evidence for action. World Health Organization, Geneva, Switzerland, 2003. Retrieved 20 September, 2019, from https://www.who.int/chp/knowledge/publications/adherence_full_report.pdf.
[2] M. Burnier, Medication adherence and persistence as the cornerstone of effective anti hypertensive therapy, Am. J. Hypertens. 19 (2006) 1190–1196.
[3] L. Nafradi, E. Galimberti, K. Nakamoto, P.J. Schulz, Intentional and unintentional medication non-adherence in hypertension: the role of health literacy, empowerment and medication beliefs, J. Public Health Res. 5 (2016) 111–115.
[4] A.L. Wroe, Intentional and unintentional nonadherence: a study of decision making, J. Behav. Med. 25 (2002) 355–372.
[5] E. Wolgast, L. Lindh-Astrand, C. Lilliecreutz, Women's perceptions of medication use during pregnancy and breastfeeding-A Swedish cross-sectional questionnaire study, Acta Obstet. Gynecol. Scand. 98 (2019) 856–864.
[6] A. Lupattelli, O. Spigset, H. Nordeng, Adherence to medication for chronic disorders during pregnancy: results from a multinational study, Int. J. Clin. Pharm. Net. 36 (2014) 145–153.
[7] J. Nachega, The effect of pregnancy on adherence to HAART among HIV-infected South African women: A pharmacy claims-based analysis. Trop. Med. Int. Health. 15 (2010);15(8) S7-S.
[8] M.J. Nielsen, M. Norgaard, P. Holland-Fisher, L.A. Christensen, Self-reported antenatal adherence to medical treatment among pregnant women with Crohn's disease, Aliment Pharm. Ther. 32 (2010) 49–58.
[9] M. Julsgaard, M. Norgaard, C.L. Hvas, D. Buck, L.A. Christensen, Self-reported adherence to medical treatment prior to and during pregnancy among women with ulcerative colitis, Inflamm. Bowel Dis. 17 (2011) 1573–1580.
[10] A.S. Lim, K. Stewart, M.J. Abramson, K. Ryan, J. George, Asthma during pregnancy: the experiences, concerns and views of pregnant women with asthma, J. Asthma 49 (2012) 474–479.
[11] C.N.H. Abheiden, A.V.R. van Reuler, W.W. Fuijkschot, J.I.P. de Vries, A. Thijs, M. A. de Boer, Aspirin adherence during high-risk pregnancies, a questionnaire study, Pregnancy Hypertens. 6 (2016) 350–355.
[12] L.A. Magee, P. von Dadelszen, E. Rey, S. Ross, E. Asztalos, K.E. Murphy, et al., Less-tight versus tight control of hypertension in pregnancy, N. Engl. J. Med. 372 (2015) 407–417.
[13] K.C. Farmer, Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice, Clin. Ther. 21 (1999) 1074–1090.
[14] A.R. Vest, L.S. Cho, Hypertension in pregnancy, Curr. Atheroscler. Rep. 16 (2014), e395, https://doi.org/10.1007/s11883-013-0395-8.
[15] S.A. Lowe, L. Bowyer, K. Lust, L.P. McMahon, M.R. Morton, R.A. North, et al., The SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014, Aust. NZ J. Obstet. Gyn. 55 (2015) 11–16.
[16] National Collaborating Centre for Primary Care: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. NICE, London; 2009.
[17] S. Garfield, S. Clifford, L. Eliasson, N. Barber, A. Willson, Suitability of measures of self-reported medication adherence for routine clinical use: A systematic review, BMC Med. Res. Method. 11 (2011), e149, https://doi.org/10.1186/1471-2288-11-149.
[18] D.E. Morisky, L.W. Green, D.M. Levine, Concurrent and predictive-validity of a self-reported measure of medication adherence, Med. Care 24 (1986) 67–74.
[19] J. George, A. Mackinnon, D.C.M. Kong, K. Stewart, Development and validation of the Beliefs and Behaviour Questionnaire (BBQ), Patient Educ. Couns. 64 (2006) 50–60.
[20] J. George, Y.T. Phun, M.J. Bailey, D.C. Kong, K. Stewart, Development and validation of the medication regimen complexity index, Ann. Pharmacother. 38 (2004) 1369–1376.
[21] M. Tomaszewski, C. White, P. Patel, N. Masca, R. Damani, J. Hepworth, et al., High rates of non- adherence to anti-hypertensive treatment revealed by high-performance liquid chromatography- tandem mass spectrometry (HP LC-MS/MS) urine analysis, Heart 100 (2014) 855–861.
[22] L.M. Webster, K. Reed, J.E. Myers, A. Burns, P. Gupta, P. Patel, C. Wiesender, P.T. Seed, N-P. C. L.C. Chappell, Quantifying adherence to anti-hypertensive medication for chronic hypertension during pregnancy. Pregnancy Hypertens. 17 (2019) 12–14.
[23] L.M. Webster, J.E. Myers, C. Nelson-Piercy, K. Harding, J.K. Cruickshank, L. Watt-Coote, et al., Labetalol versus nifedipine as anti-hypertensive treatment for chronic hypertension in pregnancy a randomized controlled trial, Hypertension 70 (2017) 915–922.
[24] V. Alves-Conceicao, K.S.S. Rocha, F.V.N. Silva, R.O.S. Silva, S. Cerqueira-Santos, M. A.P. Nunes, et al., Are clinical outcomes associated with medication regimen complexity? A systematic review and meta-analysis, Ann. Pharmacother. 54 (2020) 301–313.
[25] A. Henry, C. Crowther, Sources of advice on medication use in pregnancy and reasons for medication uptake and cessation during pregnancy, Aust. NZ J. Obstet. Gyn. 40 (2000) 173–175.
[26] E.L. Pijpers, S. Kreijkamp-Kaspers, T.M. McGuire, L. Deckx, W. Brodribb, M.L. van Driel, Women's questions about medicines in pregnancy - An analysis of calls to an Australian national medicines call centre, Aust. NZ J. Obstet. Gynaecol. 57 (2017) 334–341.
[27] V.D. Kannan, P.J. Veazie, Predictors of avoiding medical care and reasons for avoidance behavior, Med. Care 52 (2014) 336–345.
[28] J.H. Barlow, J. Hainsworth, S. Thornton, Women's experiences of hospitalisation with hypertension during pregnancy: feeling a fraud, J. Reprod. Infant Psychol. 26 (2008) 157–167.

4.3 Discussion and Summary

Nine out of ten pregnant women with a prescription for an antihypertensive were found to self-report sub-optimal adherence, confirming that prescription of an antihypertensive medication during pregnancy does not guarantee adherence. The self-reported reasons for nonadherence gave an insight into the challenges of adhering to antihypertensives during pregnancy and showed that drivers of adherence to antihypertensives in pregnancy are broader than those reported in adult hypertension. This indicates that potential interventions for the optimisation of adherence to antihypertensive medication during pregnancy should be customised to pregnancy rather than applying common interventions that are used for the adult hypertension population. One such intervention is the simplifying of antihypertensive regimens by combining more than one antihypertensive into a single tablet. This may not be useful in the pregnant population due to the changing nature of the hypertensive disorder and the consequent need for change in antihypertensive treatment. Moreover, this study illustrated that the complexity of the medication regimen does not influence adherence to antihypertensive medication in pregnant women in the same way that it does in the adult hypertensive population. Adherence to antihypertensives during pregnancy is instead influenced by the patient's understanding of risks and will be discussed further in the results of the qualitative in-depth interviews in **Chapter 5**. Asking about risk perception in the survey may have strengthened the findings and given a better insight into the factors affecting nonadherence. The role of promoting and optimising medication adherence in this population is incumbent on health professionals, including pharmacists, general practitioners and obstetricians. This is examined further in **Chapter 5**.

CHAPTER 5

ATTITUDES AND BEHAVIOURS REGARDING TREATMENT OF HYPERTENSIVE DISORDERS DURING PREGNANCY

5.1 Introduction

Chapter 4 estimated the rate of nonadherence of pregnant women who take antihypertensive medication. The survey also identified factors related to their nonadherence. A deeper understanding of the beliefs and attitudes of pregnant women towards the treatment of HDP was required to fulfil the thesis objective of gaining an understanding of medication use by pregnant women with hypertensive disorders of pregnancy, which is shared with the previous chapter.

This chapter reports research into pregnant women's attitudes and behaviours towards HDP and their treatment, undertaken in pregnant women with a diagnosis of a HDP and a prescription for an antihypertensive medication, at two tertiary maternity hospitals in Melbourne. The aim of this study was to investigate pregnant women's attitudes and behaviours towards HDP and their treatment, with a focus on providing deeper understanding of factors relating to medication adherence.

In-depth interviews were conducted with a sub-set of participants from the larger Phase 2 study (**Chapter 1**). Thematic analysis was used to discern themes that provided a rich understanding of the factors associated with attitudes, behaviours and adherence of pregnant women diagnosed with HDP and prescribed an antihypertensive, from the views of the women themselves during the pregnancy.

The results of this study have been reported in a manuscript that has been published in **SAGE Open Medicine** and is reproduced below.

Appendices relevant to this chapter are appendix 5, 6, 7, 8, 10, 12, 13, 14 and 16.

5.2 Published Manuscript: " I wish my body was stronger": A qualitative study of attitudes and behaviours regarding treatment of hypertensive disorders of pregnancy. SAGE Open Medicine. 2021;9:1–10.

Original Research Article

SAGE Open Medicine

SAGE Open Medicine
Volume 9: 1–10

DOI: 10.1177/20503121211032480
journals.sagepub.com/home/smo
SAGE

'I wish my body was stronger': A qualitative study of attitudes and behaviours regarding treatment of hypertensive disorders of pregnancy

Amyna Helou[1], Kay Stewart[1], Kath Ryan[2] and Johnson George[1]

Abstract

Objectives: To investigate pregnant women's attitudes and behaviours towards hypertensive disorders of pregnancy and their treatment.

Methods: Face-to-face, in-depth interviews were undertaken with 27 pregnant women diagnosed with and being treated for hypertensive disorders of pregnancy to investigate attitudes and behaviours regarding the conditions and their treatment. Written consent was obtained individually from each participant, and the interviews ranged from 16 to 54 minutes. Data collection was continued until thematic saturation was reached. Thematic analysis was employed to interpret the data.

Results: Four major themes emerged around beliefs and behaviours of pregnant women regarding treatment of their hypertension: understanding of hypertensive disorders of pregnancy and their implications, risks versus benefits of antihypertensive medication during pregnancy, trust in medical professionals and adherence to medication. The women's level of understanding of hypertensive disorders of pregnancy and their implications determined whether they were able to make informed decisions about their treatment. Prior experiences and concern for preservation of the pregnancy played major roles in the perception of the risk/benefit balance of using antihypertensive medication during pregnancy. The degree of trust in the treating medical professionals varied according to the perception of their confidence and knowledge.

Conclusions: Sound understanding of the condition, a positive risk/benefit balance regarding antihypertensive medication use during pregnancy, and trust in medical professionals contributed to adherence to medication. Good communication with healthcare professionals is important to achieve optimal treatment.

Keywords

Hypertension, pregnancy, obstetrics/gynaecology

Date received: 28 January 2021; accepted: 24 June 2021

Introduction

Hypertensive disorders of pregnancy (HDP) affect 10% of pregnancies in Australia[1] and are a leading contributor to maternal mortality and major morbidity worldwide.[2]

There are three main subtypes of HDP:[1] chronic hypertension, which is diagnosed either prior to pregnancy or before 20 weeks gestation. This can be either primary (no known cause) hypertension or secondary (known cause) hypertension; gestational hypertension which is diagnosed after 20 weeks gestation and preeclampsia which is defined as a multi-organ gestational disorder involving hypertension that can occur as a stand-alone disorder or superimposed on chronic hypertension. This can be either mild or severe. HELLP (Haemolysis, Elevated Liver enzymes, Low Platelet count) syndrome presents in a subset of women with severe preeclampsia with or without other preeclamptic features.

[1]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia
[2]School of Pharmacy, University of Reading, Reading, UK

Corresponding author:
Dr Johnson George, Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, VIC 3052, Australia.
Email: johnson.george@monash.edu.

Eclampsia is a rare and serious extension of preeclampsia involving maternal convulsions.[1]

Studies exploring the experiences, attitudes and behaviours of pregnant women with HDP during pregnancy have been scarce. The aspects that have been investigated include experiences of hospitalization,[3] knowledge of preeclampsia, experiences with gestational hypertension and preeclampsia, recommendations for optimal management[4,5] and the use of aspirin for the prevention of preeclampsia with a focus on good healthcare professional and patient communication.[6] Despite providing insight into these specific aspects, none of these studies were undertaken during pregnancy. There is also a paucity of studies of attitudes and behaviours regarding the use of antihypertensive medication in this population. Fear of adverse effects on the baby has been reported as a factor for medication hesitance in several studies.[7,8] Patient, socioeconomic, therapy and condition characteristics[9] all contribute to nonadherence to antihypertensives in the general adult population.[10]

Although some similarities may be drawn between the general adult population with hypertension and pregnant women, the nature of risk of uncontrolled hypertension during pregnancy is potentially a lot more imminent as it can be detrimental to the lives of both the mother and the fetus. Antihypertensive treatment is only prescribed during the pregnancy in the case of gestational hypertension/preeclampsia and is often initiated or modified during pregnancy for women with chronic hypertension.[11] It is for this reason that the experiences, behaviours and attitudes of pregnant women with HDP need separate investigation.

Our aim in this article is to investigate pregnant women's attitudes and behaviours towards HDP and their treatment. We focused on the attitudes and behaviours of pregnant women who were diagnosed with HDP and being treated with antihypertensive medication, for whom optimal adherence to medication is considered important in effective management.

Method

Study design

Qualitative in-depth interviews were conducted face-to-face with 27 pregnant women in either the second or third trimester of pregnancy, recruited from the antenatal outpatient clinics of two large tertiary maternity hospitals in Melbourne, Australia, over a 10-month period (January–October 2013).

Ethical approval

Ethical approval was obtained from Mercy Health Human Research Ethics Committee Heidelberg-Melbourne (R12/62) 08/01/2013, The Royal Women's Hospital Research and Human Research Ethics Committee Parkville-Melbourne (R13/18) 12/07/2013 and Monash University Human Research Ethics Committee Clayton-Melbourne (CF13/117) 18/01/2013.

Study sample

Participants were sourced via a larger mixed-methods study, which included 100 pregnant women with HDP. Eligible participants were identified by one researcher (A.H.) who reviewed the medical records of pregnant women attending antenatal clinics. A.H. then approached potential participants individually. Participants in the larger study responded to a questionnaire, where, on completion, they were asked to indicate their interest in undertaking an interview. Of the 98 women who responded to the questionnaire, 65 expressed interest in being interviewed. Combined convenience and purposive sampling was conducted among these 65 women to seek a breadth of views. Informed written consent was obtained prior to interview, which included permission to audio record and for quotations to be anonymously used in the reporting and publication of results. No participants dropped out of the study nor refused participation.

Participants all had a diagnosis of HDP and were prescribed antihypertensive medication. Interviews occurred during pregnancy except for one, which happened 1 day post-partum. All participants were aged 18 years or over and were fluent in English.

Data collection

Interviews were conducted by a single researcher A.H. a female Pharmacist who was a PhD candidate and had received training in in-depth interviewing prior to the commencement of the study as part of the PhD programme. The interviews were conducted using an interview guide that was based on literature[8,12] and agreed upon by the all of the authors (Box 1). As the interviewer had met the participants during the larger study, some rapport had been established prior to the interview. Participants were aware that the interviews were about their experiences with HDP. Interviews were conducted in a private room near the hospital outpatient department. Interview duration averaged 35 minutes (range 16–54 minutes).

Family members were present for some interviews but none of them participated in the interview or made comments. Socio-demographic and self-reported medical information was collected from participants through the questionnaire. Medical information was verified, with written consent, through medical records. Field notes were taken by the interviewer during the interviews. All interviews were audio-recorded, transcribed verbatim and de-identified. Interviews continued until data saturation was reached, that is, no more new information was discernible. The transcripts were not returned to the participants for comments or correction. No repeat interviews were conducted.

Box 1. Interview topic guide.

Topic one: Their hypertension
Explore the women's health beliefs surrounding their diagnosis of hypertension, e.g. when it was diagnosed and how they felt about it. Exploration into their beliefs regarding causation may also occur.
Topic two: Antihypertensive medication use during pregnancy
Explore concerns and experiences associated with the safety of using specific antihypertensive medications during pregnancy and thoughts on the importance of continuing them through pregnancy.
Investigate whether there was decreased or increased use of any particular medication and why, and factors contributing to compliance. Ask participants to compare the use of blood pressure medications to other medications during pregnancy.
Topic three: Medication beliefs
Explore the women's general medication beliefs related to the use of other medications during the current pregnancy, including over-the-counter medications, vitamins and alternative therapies, their perceived safety and benefits.

Data analysis

Data analysis occurred concurrently with the interviews. Initial coding was completed by A.H. using qualitative data management software QSR NVivo 10.[13] Inductive codes were generated systematically for the entire data set. Line-by-line analysis was then performed and nodes were created within NVivo. To ensure reliability, a random selection of 20% of the transcripts were coded independently by another member of the research team (K.S.). K.S. and K.R. read all the transcripts and differences were discussed among all three to reach consensus. The researchers were all pharmacists; K.S. and K.R. had extensive experience in conducting qualitative research. Transcripts were reread by A.H. and K.S. to ensure that coding was accurate and all relevant data were included.

Thematic analysis was employed.[14] This was done across all HDP subtypes and severities to obtain a wide breadth of views. When a pattern was seen within a certain subtype the coding was grouped specifically for that subgroup. Codes were arranged into potential themes. Themes were reviewed, refined and prepared into a final set; sub-themes were also identified within this process. In reporting, quotes are provided to illustrate the themes and the varied views of the participants. These quotes are presented in italics. The participants did not provide feedback on the findings.

Results

Participants

Twenty-seven women were interviewed to reach data saturation. Their demographics, clinical and obstetric characteristics are shown in Table 1.

Eight participants were primigravidae, the remainder were multigravidae, including six who had previous miscarriages. One participant had an assisted pregnancy (*in vitro* fertilization). Twelve were also prescribed aspirin for the prevention of preeclampsia. Participants ranged in age from 26 to 42 years.

Eighteen participants had chronic hypertension which was diagnosed before pregnancy; four of whom had secondary hypertension due to kidney disease or congenital heart disease. Nine women with chronic hypertension had their current antihypertensive regimen started during the pregnancy. Three participants had their hypertension diagnosed before 20 weeks gestation and were also classified as having chronic hypertension. Six women with chronic hypertension had developed preeclampsia superimposed on chronic hypertension at the time of the interview including one with severe preeclampsia and one with preeclampsia superimposed on secondary hypertension. Six women had gestational hypertension. All but one had developed preeclampsia at the time of interview; two of whom had developed severe preeclampsia. In total, twenty women had mild-moderate hypertensive disease whist seven had severe hypertensive disease at the time of the interview.

Interview themes

Four major themes emerged around beliefs and behaviours of pregnant women regarding treatment of their hypertension:

- Understanding of HDP and their implications;
- Risks versus benefits of antihypertensive medication during pregnancy;
- Trust in medical professionals; and
- Adherence to medication.

Understanding of HDP and their implications. Understanding of HDP as a condition varied among participants from different HDP subtypes as well as different gravidities. Some women knew a lot, others did not know but tried to find out, while others neither knew nor wanted to know.

Understanding of HDP as a condition often came from prior experience or family members' history:

> She [Obstetrician] said to me 'Go ahead with another pregnancy, because I wouldn't be that worried because your blood pressure went up at the end of the [previous] pregnancy'. . . I'm just keeping an eye on [the blood pressure potentially increasing in the third trimester]. . . because I know that that could happen. (#11, 33 years, 2nd pregnancy, second trimester, chronic hypertension)

> My Mum had high blood pressure when she had me and my brother, so I suppose it must run in the family. Wasn't really a shock. (#99, 34 years, 1st pregnancy, third trimester, late onset preeclampsia)

Table 1. Participant characteristics ($N = 27$).

Characteristics	N
Country of birth	
Australia	18
Other (India, Philippines, Nigeria, Malaysia, Indonesia, United Kingdom)	9
Ethnicity	
European	19
Asian	4
Middle-eastern	2
South-Asian	1
African	1
Co-morbid conditions	
None	16
Kidney disease	4
Depression	3
Type 2 diabetes	1
Congenital heart disease	1
Carpal tunnel syndrome	1
Rheumatoid arthritis	1
Gestational stage at interview	
Second trimester	6
Third trimester (32–34 weeks)	5
Third trimester (35–37 weeks)	6
Third trimester (⩾37 weeks)	9
1 day postpartum	1
Gestational trimester of hypertension diagnosis	
Pre-pregnancy	18
➢ Current antihypertensive regimen started during pregnancy	9
During pregnancy <20 weeks	3
At 20 weeks	0
During pregnancy >20 week	6
Subtype of hypertension[a]	
Gestational hypertension	3
Preeclampsia	3
Severe preeclampsia	2
Chronic hypertension	10
Secondary hypertension	3
Preeclampsia superimposed on chronic hypertension	4
Severe preeclampsia superimposed on chronic hypertension	1
Preeclampsia superimposed on secondary hypertension	1
Severity of hypertensive disease[a]	
Mild-moderate	20
Severe	7
Antihypertensive medication*	
Methyldopa	11
Labetalol	15
Atenolol	1
Nifedipine	1
Oxprenolol	1
Phenoxybenzamine	1

[a]Classification according to the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guidelines 2014(1).
*Eight participants were prescribed more than one antihypertensive medication.

Sound knowledge about HDP led to more informed decisions and preparedness whereas lack of knowledge led to apprehension and lack of comprehension of the seriousness of the condition. Several women with chronic hypertension were not informed of the potential implications of their hypertension during pregnancy. Some even avoided asking questions to remain oblivious to the potential implications of HDP:

> I just want to be aware, so that if I do develop full preeclampsia I know what I am in for. . . because I read how. . . when you have the baby, it can turn into eclampsia. . . I want to be able to make an informed decision. (#32, 42 years, 3rd pregnancy, third trimester, severe early onset preeclampsia)

> I didn't even hear about it [preeclampsia] to tell you the truth, I couldn't even pronounce the word when they told me [at 21 weeks gestation], what is it, I didn't know. (#71, 37 years, 2nd pregnancy, third trimester, severe early onset preeclampsia superimposed on chronic hypertension)

> No, I didn't [ask questions], no, I'm not into reading books and anything like that. . . just read little bits and pieces and just leave it up to the doctor, he can just tell me. Sometimes it's sort of like best not to know. (#22, 37 years, 3rd pregnancy, third trimester, chronic hypertension)

The perceived implications of HDP included development of preeclampsia, premature birth and intra-uterine growth restriction. The understanding of preeclampsia varied among the women. Those who understood the implications of preeclampsia were more prepared for what may happen than those who did not:

> You've just got to be prepared, I guess. I prefer to know about it [preeclampsia] than to not know about it and if there is something I could do to maybe prevent it, then best to have it [medicine]. (#2, 30 years, 1st pregnancy, third trimester, secondary chronic hypertension)

> It's an unknown so that's why it does worry me. . . I know of people who have had preeclampsia and they have had to have their babies really early, which is less stressful for me. . . going back to 30 weeks kind of was a worry that if that did happen to me, something could go wrong and then I would have to bring the baby on early and. . . all the complications that come with that. (#19, 26 years, 1st pregnancy, third trimester, chronic hypertension)

Many women did not have a sound understanding of the risk of premature birth. Some were surprised to be told that they would potentially need to be delivered earlier than full term, while others had to find their own information:

> I guess I was like a little bit sort of surprised at the time [when the obstetrician mentioned it] to think, oh gee, I really might not go full term. (#21, 35 years, 1st pregnancy, second trimester, chronic hypertension)

> After I did my research I stumbled across the preeclampsia. . . I was reading that if you do develop preeclampsia that the baby may need to be induced quite early. . . because it is a risk for the baby if you do develop that. It's a risk to the mother as well, because you can actually go into a coma. (#24, 35 years, 1st pregnancy, third trimester, chronic hypertension diagnosed during pregnancy before 20 weeks gestation)

The potential for intra-uterine growth restriction was mostly understood. Some exhibited fear while others considered it as a matter of fact:

> What I am afraid of, if I develop preeclampsia, is that the blood flow through the placenta doesn't get affected so that the baby doesn't get affected. (# 21, 35 years, 1st pregnancy, second trimester, chronic hypertension)

> I had a scan on Thursday and the baby is. . . not growing at the same rate it should, so it's gone from 50, 35 to 20th percentile. . . it's because [of the] blood pressure. . . the blood doesn't pass through your placenta properly. (#74, 36 years, 2nd pregnancy, third trimester, chronic hypertension)

Some women felt overwhelmed by the volume of information that they received from the treating team and often needed more time to process it before being able to ask any questions. Others felt confused and resorted to using the Internet as a source of information:

> So. . . it took me a while to get my head around being in hospital. There I was. . . on the labetalol straight away and then all blood tests and neuro tests and steroids and it was all just bang, bang, bang, happening quite fast. . . then it was after, when I went home and I was able to rest. . . that I could think about more questions that I wanted to ask. (#32, 42 years, 3rd pregnancy, third trimester, severe early onset preeclampsia)

> I often get very confused when I'm in seeing the doctors and I get a bit overwhelmed and I don't ask a lot of questions, and then I kind of come away thinking 'I wish I'd asked that question and really pushed the answer'. And then usually I take to Googling it, which is always the worst. (#41, 34 years, 1st pregnancy, third trimester, late onset preeclampsia superimposed on secondary chronic hypertension)

Conflicting information from various medical professionals often led to confusion:

> I saw someone different every time I went. . . and it was all real higgledy, piggledy information. I never got the same information from the same person, which was really, really hard. (#74, 36 years, 2nd pregnancy, third trimester, chronic hypertension)

> They said it [aspirin] helps with blood pressure, and they said that I had to start taking them. . . but the thing is that one doctor told me to take it this many weeks and then another one told me to take it this many weeks, and supposedly I started taking it too late. So, I don't know. . . I kind of rounded it off in the middle and it was wrong. (#90, 35 years, 7th pregnancy, third trimester, chronic hypertension)

Risks versus benefits of antihypertensive medication during pregnancy. After being prescribed antihypertensive treatment during pregnancy, many women assessed the risk versus benefit balance in the context of the baby being their priority. For some, taking the medication was perceived as preserving the pregnancy and allowing longer gestation time. The short-term nature of antihypertensive use in gestational hypertension also positively affected their decision to take the medication:

> I mean, emotionally you feel pretty bad taking medication. . . I've often felt really bad for her [the baby]. Like I've always said, I've been a terrible vessel for her. . . I wish I was better. . . I wish my body was stronger to be able to do it for her, but. . . at the same time, the medication has gotten me through so that I can have her so, you know, it's a weigh up. (#41, 34 years, 1st pregnancy, third trimester, late onset preeclampsia superimposed on secondary chronic hypertension)

> I have only ever thought 'Oh it's only for a short time'. I can do it because it's only for such a short time. . . I can do it. It's just like 10, 12 weeks or so. I can do this'. (#6, 28 years, 4th pregnancy, 1 day postpartum, gestational hypertension)

Others had concerns about the effect of antihypertensive medications on the baby and feared a potentially negative impact. Some were prescribed a medication that was not safe during early pregnancy but wanted to avoid uneasiness and were content with oblivion:

> I asked the midwife and even the doctor. . . 'will it [the antihypertensive] affect my baby, because I am very concerned taking so many hypertensive drugs, and I am just afraid that something might happen to my baby'. And then they said 'No, no nothing will happen to your baby. because those drugs have been given [safely]. . . for pregnant women'. (#14, 40 years, 2nd pregnancy, second trimester, severe early onset preeclampsia)

> I wonder actually [about the potential effect of atenolol during the first trimester]. . . but I don't want to stress myself also because I'm scared that if I ask this kind of question and then they start telling me about 'Oh the baby might have this might have that'. . . in the end I will get stressed and. . . I won't be able to continue my pregnancy. . . in a relaxed condition. So sometimes I find that oblivious can be quite a good [thing]. (#59, 34 years, 1st pregnancy, second trimester, chronic hypertension)

The Internet was a source of information for many of the women regarding the risk versus benefit balance of antihypertensives during pregnancy. Women were mostly vigilant in finding the most appropriate Internet source while others were less cautious. The consumer medicines information leaflets (CMI) for the antihypertensives were another source of information. Concerns were voiced about the CMI for

labetalol,[15] as it contained information conflicting with other sources of information. One participant expressed her concern of the baby coming out 'green and glowing':

> Just have a look which ones are good ones [internet sites], you know reputable. . . whether it's by. . . a government agency, whether it's got actual medical. . . people speaking on there, where their references come from. If you cross check it against other sites and they say similar things. If there's someone, or an agency or a body that you've heard of that you think would be. . . one that you could trust. (#99, 34 years, 1st pregnancy, third trimester, late onset preeclampsia)

> [The labetalol CMI] was really concerning because it says let your doctor know if you're pregnant. . . there's not that much information out there on Google about it [so next time I saw the doctors I asked] is there any side effects with the labetalol and they said no, none whatsoever, so I had to just trust in that. (#32, 42 years, 3rd pregnancy, third trimester, severe early onset preeclampsia)

Prior experience with HDP also influenced opinion of the risk versus benefit balance. Fears of a sudden increase in blood pressure, even when it was low, gestational timing of taking the medication and previous uncontrolled blood pressure and preeclampsia brought back undesirable memories:

> My only worry is that, with my first pregnancy, I started the tablets when the baby was all developed and ready to come out, and this time I'm taking the tablets from the beginning of the pregnancy. (#11, 33 years, 2nd pregnancy, second trimester, chronic hypertension)

> Ooh, I don't want medicine but I was like 'Ooh medicine/neonatal intensive care unit?; medicine/neonatal intensive care unit? – I decide medicine'. . . It wasn't really a big hard decision. I mean, I'd been in the neonatal intensive care unit with [third child] and [visited] our friend's little girl. . . I didn't want to go back there. (#6, 28 years, 4th pregnancy, 1 day postpartum, gestational hypertension)

Trust in medical professionals. Many women expressed trust in their treating doctors. The doctor's medical knowledge and professional experience were given as reasons to trust them and not question further. Some participants briefly questioned the need for medications but trust in the doctor led them to take the medication:

> I didn't do any research only because I trust, I had trust in the doctors. . . it's confidence. . . that they know obviously what they're doing. They've had their medical certificates for many, many years. (#8, 36 years, 2nd pregnancy, third trimester, chronic hypertension)

> You would trust that doctors aren't going to put you on anything that is going to harm the baby and that you are seeing the specialists who know what you can and can't have. (#5, 38 years, 5th pregnancy, third trimester, gestational hypertension)

Women differentiated between doctors on their perception of the professional's level of experience when it came to the prescribing of the antihypertensive. Differing medical opinions sometimes caused lack of confidence in a doctor's advice and at times, lack of trust. This was sometimes linked to the woman's unfamiliarity with a doctor, when multiple doctors are involved in the patient's care. An impression that the doctor was not confident also resulted in lack of trust:

> He [physician] said 'At this stage your reading is okay. . . however, you know you may need to go on blood pressure tablets later on during the pregnancy'. [then] I was having a baby monitoring test. . . and a doctor that I didn't know. . . came in and, because of the blood pressure readings, decided that I should go on the medication. . . I hesitated at first. . . because of the fact that the physician who specializes in blood pressure ruled it out at that stage. I felt a little bit uncomfortable with a doctor I didn't know saying I should go on them. (# 24, 35 years, 1st pregnancy, third trimester, chronic hypertension diagnosed during pregnancy)

> I went down to the Emergency section and then they had my file but they kept asking me 'Oh, ok so you don't have any blood pressure problems?' and I am like 'No you've got my file in front of you and it says I have got blood pressure problems and I am on pills'. . . I don't know. . . I just wasn't confident in what she said and I wasn't sure really that doubling it [the antihypertensive dose] was [a good idea]. . . she just kept asking me the same thing. . . I just wanted to talk to someone who was going to say 'Doubling is what you should do'. (#2, 30 years, 1st pregnancy, third trimester, secondary chronic hypertension)

Community pharmacists were a valuable source of information for some women. Others, however, had found that pharmacists were not confident with their knowledge regarding medication use during pregnancy:

> I was told not to [look at the Internet] and I always ask the chemist or I ask my doctor what else I could take and I couldn't take anything. (# 1, 39 years, 2nd pregnancy, third trimester, secondary chronic hypertension)

> I find out if you're asking something, the pharmacist – you do ask them. . . and they're good, but some of them they keep searching on the internet forever. It's better if you search on the internet [yourself]. (#81, 34 years, 1st pregnancy, second trimester, chronic hypertension)

Adherence to medication. Women with chronic hypertension who were complacent about taking antihypertensives before pregnancy started to improve adherence to their medication for the safety of the baby. Some women with gestational hypertension believed that they had no choice but to take the prescribed treatment. Worsening of blood pressure was also an incentive to take the antihypertensive medication. Safety concerns, however, resulted in intentional nonadherence to aspirin by some women:

I took it straight away because it was for blood pressure. . . if something happens inside or he gets taken out early, either way I don't really have much of a choice. . . but it wasn't the doctors saying I don't have a choice, it was my head telling me I don't have a choice. (#6, 28 years, 4th pregnancy, 1 day postpartum, gestational hypertension)

I really worried about taking the aspirin, and they had prescribed it to me before my 12 weeks and had told me to start taking it. . . I refused to take it; I just didn't tell them. I just stopped – wouldn't take it until I was 12 weeks. I was really worried about taking it before the 12 weeks. (#41, 34 years, 1st pregnancy, third trimester, late onset preeclampsia superimposed on secondary chronic hypertension)

Adverse effects from the antihypertensives resulted in intentional nonadherence by some women. Others were hesitant to stop taking the antihypertensive despite adverse effects:

I took it [methyldopa]. . . it made me sick, so I stopped taking it. (#90, 35 years, 7th pregnancy, third trimester, chronic hypertension)

They weaned me off that [oxprenolol] very early. I am thinking by about 20 weeks I was off it. . . I didn't need to take it basically. . . My heart rate was very low and they didn't want my heart rate to be that low. . . No. I never thought of just stopping it. I asked the specialist and she said I couldn't just stop it like that. (#1, 39 years, 2nd pregnancy, third trimester, secondary chronic hypertension)

Some women perceived taking the antihypertensive as an interference to their lifestyle. There were those who could not see how to incorporate the antihypertensive regimen into their daily routine and others who were resistant to change:

Because now, after I got pregnant, the doctor changed the medicine to oxprenolol, and oxprenolol is twice a day. Atenolol is once a day. . . I always remember before I sleep I would take one. . . But normally in the morning, I'm busy – tidy house, breakfast, watch TV. That's already one o'clock, then I already miss a time, so I skip them again. I would just take the night [dose]. (#59, 34 years, 1st pregnancy, second trimester, chronic hypertension)

I didn't know what kind of medication and what kind of changes I would have to make. . . I didn't want to change my lifestyle. I love my lifestyle, I love food. . . it was more that I didn't want to change that. (#18, 35 years, 2nd pregnancy, second trimester, chronic hypertension)

Significant others were a source of encouragement in several cases, whereas some significant others would challenge the woman to re-evaluate her need for the medication:

It's alright, get up in the morning – because I've got two kids I'm home anyway – so I'm usually up in the morning. So whatever time I get up, on average about 8 o'clock is usually when I take it, and then lunchtime about 3 or 4, before I go to bed about 11. So, we space it out so it's like an eight-hour gap in between each one. . . and if I forget my husband reminds me. (#64, 30 years, 3rd pregnancy, third trimester, chronic hypertension)

Well I think my partner put it perfectly. . . he said 'I don't know if I like you taking the medication because it's sort of tricking your body into doing something'. . . just after taking it, within those first couple of hours I have got a lot of energy. And he said 'You know, is it really that good that you are taking it?' Isn't it better that they see the true picture, you know, because often I will come in here, only a couple of hours after taking the tablet, and the blood pressure is down. (#5, 38 years, 5th pregnancy, third trimester, gestational hypertension)

Unintentional nonadherence in the form of forgetting to take the medication was seen in many women. Some would ask for advice when they forgot a dose. Others used adherence aids like pill boxes to help them:

I have breakfast, and try taking them at night before I go to bed, and lunch time. . . but I forget sometimes. . . you get busy through the day. . . and I forget, especially when I'm at work. . . and even this morning, I normally take them with breakfast, but then I took my daughter to the childcare and I'm like 'Oh I haven't taken any of my med.'. . . Oh well, I took them when I got home. But it's just. . . life isn't it? (#74, 36 years, 2nd pregnancy, third trimester, chronic hypertension)

I think the chemist doctor person would have, like, enough knowledge to give me an educated description of what to do [after I forgot to take the dose]. (#6, 28 years, 4th pregnancy, 1 day postpartum, gestational hypertension)

Pillbox. Otherwise I don't remember. I do them at the same time every day, as soon as I wake up in the morning take the blood pressure and then take the pill, at dinner take the pill, take the blood pressure take the pill, so try and remember. (#2, 30 years, 1st pregnancy, third trimester, secondary chronic hypertension)

Discussion

This study is the first to explore pregnant women's attitudes and behaviours towards their HDP and its treatment during pregnancy using in-depth interviews and to be analysed from a pharmacist perspective.

Previous HDP, family history and obtaining information from a healthcare professional or the Internet facilitated understanding of the implications of HDP. This is similar to a study which found that higher literacy, multiparity, history of preeclampsia and receipt of information about preeclampsia from a clinician or another information source (e.g. the Internet, television, books or friends) were factors associated with a greater proportion of correct answers on a survey of 25 questions assessing knowledge of preeclampsia; however, patients only answered an average of 43% correctly.[4]

Those with sound knowledge were more prepared for the possibility of the progression of the HDP and emergence of implications, namely preeclampsia, premature birth and intra-uterine growth restriction. This allowed them to make more confident decisions when it came to treatment of HDP and to plan for the care of children they already had. In our study, those who were not aware of the implications of HDP on the baby had not been offered information about the risks, nor did they ask or search for any information. This was mainly seen in those with pre-existing chronic hypertension. Women only became aware of the risks when their blood pressure was already high or when they were showing signs of preeclampsia. In contrast, those who had secondary chronic hypertension were well-informed and prepared for the potential complications of HDP. This may imply that the latter group were informed of the risks prior to pregnancy by their treating doctors, whereas those with primary chronic hypertension were not.

The volume of available information at the time of diagnosis of gestational hypertension/preeclampsia was deemed overwhelming at times. This information was often given verbally by the treating team thus not allowing the patient to review the advice at a later date nor reference the information when being faced with conflicting advice from different healthcare professionals. Many women did not know that low-dose aspirin was prescribed to prevent preeclampsia and assumed that it was for blood pressure. This led to some intentional nonadherence due to safety fears during the first trimester. Since the time of patient recruitment to this study, one of the research sites has produced a fact sheet explaining preeclampsia and the use of low-dose aspirin in prevention.[16] Although it is not yet known how this has impacted patient understanding, it would be expected to yield some reassurance for women at risk of developing preeclampsia, thus allowing them to make more informed decisions about their treatment.

The balance of risk versus benefit regarding antihypertensive medication during pregnancy was related to the patient's understanding of the information that she had access to, as well as her previous experiences. As previously mentioned, some women felt overwhelmed by the volume of information or were confused by differing advice from various doctors. This limited the woman's ability to make a sound risk versus benefit decision but trust in the treating doctor encouraged most women to take the antihypertensive. Previous experiences with HDP facilitated the balance of risk versus benefit often resulting in the decision to take the medication as prescribed. The severity of the hypertension/preeclampsia as well as the stage of pregnancy at the time of the interview also impacted on the women's decision. Those who understood the risk of early premature birth also had a better grasp of this balance. A recent study of health beliefs about medicines in pregnancy found that nearly half of the women were worried about the effects of a medication when they used it for a long period.[17] In our study, women with gestational hypertension who had a shortened length of antihypertensive treatment perceived this as an incentive to take the medication as prescribed. Women with gestational hypertension who were prescribed the antihypertensive after 20 weeks gestation also did not have the burden of first trimester medication safety concerns.[7]

The consumer medicine information leaflet for labetalol caused understandable angst among some women because of the statement 'Do not take this medicine if you are pregnant'.[15] This deterred some women from taking it until they were able to clarify with their treating doctor, whereas others were confused by conflicting advice and decided not to take the medication. Both clinical and community pharmacists have a role to play in the clarification of this perplexity. Community pharmacists, in particular, are readily accessible for advice. Similarly, the treating doctor is in a position to explain the reason for the warning in the CMI but reassure the patient about the safety of labetalol. A strong healthcare professional/patient partnership can facilitate patient understanding and allow clarification of concerns to provide assurance around the safety and role of antihypertensive medications in the treatment of HDP.[6]

Trust in the treating doctor was expressed by many of the women and it convinced most women to take their antihypertensive. This was observed at a higher rate than may have been expected given the age of the participants and the influence of the Internet on the decision-making process. It should be remembered that many participants were experiencing a high-risk pregnancy, with the possibility of sudden negative changes to their state of health and that of their baby at any time during the pregnancy.[1] Some, especially those with gestational hypertension or preeclampsia, also had to cope with a new diagnosis of an urgent serious condition, often with little or no immediate symptoms.[1,3] This has previously been reported in patients who were informed of a cancer diagnosis. Patients diagnosed with pancreatic cancer reported that they perceived themselves as having no choice in treatment of the condition in light of the new, urgent and life-threatening situation, but that trust in the treating doctor was paramount.[18] The self-reported trusting nature of some of our participants supported their decision to take the antihypertensive medication as prescribed, without feeling the need to search for other sources of information for reassurance.

Lack of confidence in the doctor's advice was observed when there were conflicting medical opinions. This resulted in confusion for the patient with some taking the advice of the treating doctor and others waiting to see the initial treating doctor before making the decision to take the medication. Similarly, some of the women were later treated by unfamiliar doctors, resulting in a lack of trust. Seniority in terms of their experience engendered trust in the treating doctor; thus, when a doctor showed lack of confidence in the treatment of the patient, this was followed by lack of trust. In an Australian qualitative study by midwives on the experiences of women who had gestational hypertension or preeclampsia during pregnancy the authors argued that a

multidisciplinary, collaborative, continuity of care model should be provided to women in a high-risk pregnancy such as gestational hypertension and preeclampsia.[5] Furthermore, improved continuity of care has been found to result in higher medication adherence in the general adult population in conditions such as type 2 diabetes.[19]

Community pharmacists were a valuable source of information for some women. Others, however, found that pharmacists were not confident with their knowledge regarding hypertension in pregnancy. This can result in conflicting advice as observed in a study of adherence to aspirin in the prevention of preeclampsia.[6]

The decision of each woman to adhere to antihypertensive medication was influenced by her individual understanding of HDP and its implications, her risk versus benefit analysis and her trust or lack thereof in her treating doctor. These themes are largely consistent with those identified in the World Health Organization (WHO) publication 'Adherence to Long-term therapies: Evidence for Action', namely: patient (20%), socioeconomic status (20%), condition (20%), therapy (20%) and healthcare team/healthcare system (20%).[9] The women who had a sound understanding of the risks were aware that adherence to the antihypertensive would be of benefit to both themselves and their unborn babies. There were, however, others who did not want to take their antihypertensive medication as they were not aware that consistently high blood pressure could be harmful for the baby. Improved understanding of the risks of uncontrolled blood pressure during pregnancy and good communication between the patient and the healthcare team can promote adherence in this group of women. Partner support during pregnancy has been well documented as having a pivotal role in social and psychological support.[20] A partner with limited knowledge about potential risks of HDP may not recognize warning signs of the condition and may not pursue care for his pregnant partner in a timely manner.[21] In this regard, it may be valuable to involve the partner in the discussion of the potential risks of HDP. Similarly, involving the partner in the discussion around treatment of HDP can potentially assist the woman if she is overwhelmed with information and also to clarify any questions/misconceptions that the partner may have surrounding the HDP. This may enable the patient to have a clearer understanding of the risks of HDP and risks versus benefits in taking the medication, thus facilitating better adherence. Significant others were also seen as facilitators for adherence when reminding women to take the antihypertensive when they might have forgotten a dose.

Adverse effects, which were the cause of medication discontinuation in some women, could be discussed with the treating team in an open way. Good communication between the patient and the healthcare team increases trust,[6] facilitating the conversation with the doctor to potentially alter the medication to a more suitable agent, thus helping adherence. Community pharmacists can also assist with supplying adherence aids to those who are on multiple medications and have unintentional nonadherence.

In closing, we recommend that women of child bearing age with chronic hypertension be informed by their general practitioner of the risks of chronic hypertension during pregnancy, including an increased risk of preeclampsia. They should also be advised that their antihypertensive be changed to a safer one when planning pregnancy or as early as possible in the pregnancy. Community pharmacists can assist in initiating the conversation of switching to a safer antihypertensive if pregnancy is being planned. Pharmacists may also help to reassure women of the safety of labetalol during pregnancy by going through the consumer medicine information with them during counselling. Pharmacists are in a unique position, as accessible first line health professionals, to be a trusted source of information for women with HDP but might have limited experience in the field and require further training. Training should also be provided to emergency department doctors in maternity hospitals regarding the relevant treatment protocols followed by physicians and obstetricians for managing HDP. This could assist in providing a unified approach to treatment for such women, thus facilitating trust and adherence.

Our study included women with all forms of HDP except HELLP and eclampsia, as the interviews were done when the women were in a comfortable, non-emergency situation. Recruitment was from two major public maternity referral hospitals in Melbourne with a widespread combined catchment including metropolitan, regional and rural areas. Participants varied in gestation stage, subtype of HDP, severity of HDP, ethnicity and socioeconomic status allowing for a wide range of views. The interviews and analyses were conducted by researchers from a pharmacy background and all had extensive experience working in interdisciplinary teams. The interviews were conducted during pregnancy thus reducing recall bias. This is in contrast to other qualitative studies which explored aspects of HDP in retrospect.[3,5,6]

Limitations of the study. Participants did not include those in the first trimester of pregnancy, as most were scheduled to attend the antenatal clinics after 12 weeks gestation. Views of women with chronic hypertension during the first trimester of pregnancy may vary from those in the second and third trimesters. Women with poor English skills were excluded from the study, therefore, caution should be taken in the extrapolation of our findings to women from non-English speaking backgrounds. Having both sites in only one city was, however, a limitation to extrapolating the results beyond Melbourne.

Conclusion

Pregnant women with HDP have varied understanding of the condition and the need for treatment. Good communication with healthcare professionals may help build trust contributing to conversations that result in better understanding. Attention needs to be paid to the concerns of the patient, both in terms of the condition and its risks as well as concerns around treatment. Obstetricians, midwives, general practitioners and community

pharmacists can help bridge the knowledge gap and offer counselling to resolve concerns hindering adherence to HDP treatment.

Acknowledgements

We would like to thank the staff at both the Mercy Hospital for Women and the Royal Women's Hospital for their help with this study. We would also like to thank all the women who participated in this study.

Author contributions

All authors contributed to the conception and design of the study. Patient recruitment and in-depth interviews were undertaken by A.H.. Data analyses and interpretation were performed by A.H., K.S. and K.R.. The manuscript was written by A.H. and critically reviewed by all authors. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from Mercy Health Human Research Ethics Committee Heidelberg-Melbourne (R12/62), The Royal Women's Hospital Research and Human Research Ethics Committee Parkville-Melbourne (R13/18) and Monash University Human Research Ethics Committee Clayton-Melbourne (CF13/117).

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from all subjects before the study.

ORCID iDs

Amyna Helou https://orcid.org/0000-0002-4162-0711

Johnson George https://orcid.org/0000-0002-0326-0495

References

1. Lowe SA, Bowyer L, Lust K, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. *Aust NZ J Obstet Gyn* 2015; 55(5): e1–e29.
2. World Health Organisation. *The World Health Report 2005: Make every mother and child count*. 2005, https://www.who.int/whr/2005/en/ (accessed 6 November 2020).
3. Barlow JH, Hainsworth J and Thornton S. Women's experiences of hospitalisation with hypertension during pregnancy: feeling a fraud. *J Reprod Infant Psyc* 2008; 26(3): 157–167.
4. You WB, Wolf M, Bailey SC, et al. Factors associated with patient understanding of preeclampsia. *Hypertens Pregnancy* 2012; 31(3): 341–349.
5. Roberts LM, Davis GK and Homer CS. Pregnancy with gestational hypertension or preeclampsia: a qualitative exploration of women's experiences. *Midwifery* 2017; 46: 17–23.
6. Shanmugalingam R, Mengesha Z, Notaras S, et al. Factors that influence adherence to aspirin therapy in the prevention of preeclampsia amongst high-risk pregnant women: a mixed method analysis. *PLoS ONE* 2020; 15(2): e0229622.
7. Nordeng H, Ystrom E and Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. *Eur J Clin Pharmacol* 2010; 66(2): 207–214.
8. Lim AS, Stewart K, Abramson MJ, et al. Asthma during pregnancy: the experiences, concerns and views of pregnant women with asthma. *J Asthma* 2012; 49(5): 474–479.
9. Sabate E (ed.) *Adherence to long-term therapies: evidence for action*. Geneva: World Health Organization, https://www.who.int/chp/knowledge/publications/adherence_full_report.pdf (accessed 20 September 2020).
10. Burnier M and Egan BM. Adherence in hypertension a review of prevalence, risk factors, impact, and management. *Circ Res* 2019; 124(7): 1124–1140.
11. Helou A, Walker S, Stewart K, et al. Management of pregnancies complicated by hypertensive disorders of pregnancy: could we do better? *Australia New Zealand J Obstetric Gynaecol* 2017; 57(3): 253–259.
12. Sawicki E, Stewart K, Wong S, et al. Medication use for chronic health conditions by pregnant women attending an Australian maternity hospital. *Aust N Z J Obstet Gynaecol* 2011; 51(4): 333–338.
13. Microsoft Windows NVivo 10, http://help-nv10.qsrinternational.com/desktop/concepts/about_nodes.htm (accessed 21 February 2020).
14. Braun VCV. Using thematic analysis in psychology. *Qual Res Psychol* 2006; 3(2): 77–101.
15. NPS Medicine Wise. Presolol (Labetalol) Consumer Medicines Information leaflet (CMI), https://www.nps.org.au/medicine-finder/presolol-tablets (accessed 15 August 2020).
16. The Royal Womens Hospital. Explaining Preeclampsia 2018, https://thewomens.r.worldssl.net/images/uploads/fact-sheets/Preeclampsia-2018.pdf (accessed 14 July 2020).
17. Nugraheni G, Sulistyarini A and Zairina E. Beliefs about medicines in pregnancy: a survey using the beliefs about medicines questionnaire in Indonesia. *Int J Clin Pharm* 2020; 42(1): 57–64.
18. Schildmann J, Ritter P, Salloch S, et al. 'One also needs a bit of trust in the doctor . . .': a qualitative interview study with pancreatic cancer patients about their perceptions and views on information and treatment decision-making. *Ann Oncol* 2013; 24(9): 2444–2449.
19. Chen C, Tseng C and Cheng S. Continuity of care, medication adherence, and health care outcomes among patients with newly diagnosed Type 2 diabetes A longitudinal analysis. *Med Care* 2013; 51(3): 231–237.
20. Kotelchuck M and Lu M. Father's role in preconception health. *Matern Child Health J* 2017; 21(11): 2025–2039.
21. Mellon M, Schiller A, Nelson AL, et al. Awareness of pregnancy-associated health risks among pregnant women and male partners surveyed in a prenatal clinic. *J Womens Health* 2020; 29(3): 376–382.

5.3 Discussion and Summary

The information gained by interviewing the women in depth has given a rich understanding of the factors associated with the attitudes, behaviours and adherence of pregnant women diagnosed with hypertensive disorders of pregnancy and being treated with antihypertensive medication and agents to prevent pre-eclampsia, including low-dose aspirin. Sound understanding of the condition, a positive risk/benefit balance regarding medication use for HDP, and trust in medical professionals were found to contribute to adherence to medication. These factors had not been previously reported in this population nor are they identifying factors for optimising adherence to general adult hypertension medications. The study also demonstrated that the role of promoting and optimising medication adherence in this population is incumbent on health professionals, including pharmacists, general practitioners and obstetricians. This information will help to inform future strategies for optimising treatment in-practice.

The in-depth nature of the interviews allowed for a wide breadth of views to be expressed by the participating women. This allowed the fulfilment of the thesis objective to not only understand the women's perspectives on adherence to medication, but also to understand their perspectives on the clinical management of their HDP. Views of the patient's clinical management journey were voiced and are detailed in the following chapter, **Chapter 6**.

CHAPTER 6

WOMEN'S EXPERIENCES WITH THE MANAGEMENT OF HYPERTENSIVE DISORDERS OF PREGNANCY

6.1 Introduction

Attitudes and behaviours towards the use of medication and adherence were expressed in the in-depth interviews and described in the previous chapter, **Chapter 5**. This gave a deep insight into the factors and perceptions associated with medication taking and adherence in women who are prescribed antihypertensive medication for the treatment of their HDP. Further to this, the in-depth interviews provided an overall view of the experiences of these women with the clinical management of their HDP, fulfilling the second part of the third objective of the thesis, which was to understand the women's perspectives on adherence to medication and the management of their hypertensive disorder of pregnancy.

This chapter reports research into the perspectives and experiences of women regarding clinical management of their HDP, which was undertaken in pregnant women with a diagnosis of HDP and a prescription for an antihypertensive medication at two tertiary maternity hospitals in Melbourne. The aim of this study was to investigate pregnant women's experiences with clinical management of hypertensive disorders of pregnancy.

The in-depth interviews were the same Phase 2 interviews as reported in **Chapter 5**. Some of the themes discerned by thematic analysis were related to attitudes and behaviours towards medication use and adherence, whilst the rest were on the topic of clinical management. The women's perspectives about their clinical management gave an overall insight into their experiences, from the views of the women themselves during pregnancy.

The results of this study have been reported in a manuscript that has been published in **BMC Health Services Research** and is reproduced below.

Appendices relevant to this chapter are appendix 5, 6, 7, 8, 10, 12, 13, 14 and 16.

6.2 Published manuscript: Pregnant women's experiences with the management of hypertensive disorders of pregnancy: a; qualitative study.
BMC Health Services Research.2021;21:1292

Helou *et al. BMC Health Services Research* (2021) 21:1292
https://doi.org/10.1186/s12913-021-07320-4

BMC Health Services Research

RESEARCH Open Access

Pregnant women's experiences with the management of hypertensive disorders of pregnancy: a qualitative study

Amyna Helou[1], Kay Stewart[1], Kath Ryan[2] and Johnson George[1*]

Abstract

Background: Hypertensive disorders are a leading cause of mortality and morbidity during pregnancy. Despite multiple national and international clinical guidelines and a plethora of research in the field of optimising management, there has been limited research describing the perspectives and experiences of pregnant women with the management of hypertensive disorders of pregnancy (HDP). Understanding these perceptions and experiences is imperative to the optimisation of HDP management.

Methods: A qualitative study involving face-to-face, in-depth interviews were undertaken with 27 pregnant women diagnosed with and being treated for HDP to explore their perspectives of and experiences with clinical management. Written consent was obtained individually from each participant, and the interviews ranged from 16 to 54 min. Inductive codes were generated systematically for the entire data set. Line-by-line analysis was then performed and nodes were created within NVivo, a qualitative data management software. Data collection was continued until thematic saturation was reached. Thematic analysis was employed to interpret the data.

Results: Three major descriptive themes were discerned regarding the women's perspectives on and experiences with the management of HDP: attitudes towards monitoring of HDP, attitudes and perceptions towards development and management of complications, and perceptions of pregnant women with chronic hypertension. Trust in the hospital system, positive attitudes towards close blood pressure monitoring as well as self-monitoring of blood pressure, and a realistic approach to emergency antenatal hospital admissions contributed to a positive attitude towards monitoring of HDP. Women with prior experiences of HDP complications, including pre-eclampsia, were more confident in their clinical management and knew what to expect. Those without prior experience were often in shock when they developed pre-eclampsia. Some women with chronic hypertension displayed limited understanding of the potential risks that they may experience during pregnancy and thus lacked comprehension of the seriousness of the condition.

Conclusions: The clinical management experiences of pregnant women with HDP were varied. Many women did not feel that they were well informed of management decisions and had a desire to be more informed and involved in decision-making. Clear, concise information about various facets of HDP management including blood pressure monitoring, prescription of the appropriate antihypertensive agent, and planning for potential early delivery are required.

*Correspondence: johnson.george@monash.edu
[1] Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, Melbourne, Victoria, Australia
Full list of author information is available at the end of the article

Keywords: Pregnancy, Hypertension, Chronic hypertension, Pre-eclampsia, Experiences, Management

Introduction

Hypertensive disorders of pregnancy (HDP) affect around 10% of pregnancies in Australia and around the world [1]. Combined, they are the second largest cause of maternal death, after haemorrhage, in the developed world [1].

In Australia, the public health system provides maternity care from pre-conception to postpartum. The main health professionals who care for the pregnant women are obstetricians, midwives, general practitioners (GP) and obstetric physicians [1]. The GP has an important role in pre-conception counselling, especially with women who have chronic diseases such as hypertension or asthma. It is also the responsibility of the GP to confirm the pregnancy and refer the woman to the relevant maternal hospital service.

Initially, the choice of model of care is given to the woman. The Midwifery Group Practice model [1] allows for one-to-one maternal care, often with the same midwife throughout the term of pregnancy, which is a suitable option for women without complications. Pregnant women with complications such as chronic hypertension or a previous pregnancy complicated by hypertensive disorders of pregnancy (HDP), however, need to be cared for by an obstetrician, who can monitor the progress of the pregnancy, blood pressure (BP), signs of pre-eclampsia, and fetal growth. The obstetric physician is usually involved in prescribing and monitoring antihypertensive medication and BP control. Pregnant women who have had pre-eclampsia previously or who have chronic hypertension are at risk of developing pre-eclampsia. Timely administration of low-dose (81-100 mg) aspirin before 16 weeks gestation has been found to reduce risk of pre-eclampsia [2].

Monitoring of BP occurs at each antenatal visit. If her BP is elevated, the woman may be referred to a day assessment unit for 4-h assessment of BP, which involves taking BP readings every half an hour for 4 h to observe the pattern of the BP and decide whether a diagnosis of HDP and/or prescription of an antihypertensive medication is warranted. In addition, test for urinary protein, full blood examination, renal function tests and fetal monitoring are performed [3]. This 4-h assessment is seen as a favourable alternative to overnight inpatient stays, both in terms of patient satisfaction and public health economics [3].

The timing of delivery in women with HDP is dependent on many maternal and fetal factors, including inability to stabilise BP, deteriorating liver and/or renal function, placental abruption, and severe fetal growth restriction [4]. Fetal morbidity and mortality are linked to the gestational age at delivery [4], so there is always a desire to prolong the pregnancy as close as possible to term (37 weeks) in the absence of an emergency. HYPITAT was a multicentre, open-label randomised controlled trial investigating induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation [5]. The study reported a reduction in the incidence of severe hypertension as result of induction of labour at 36 weeks gestation. No significant clinical differences were found in outcomes such as thromboembolism, eclampsia or placental abruption [5]. This study was followed by HYPITAT-II, which found that delivery should be deferred until 37 weeks as opposed to 36 weeks, unless maternal deterioration supervenes [6].

Despite multiple clinical guidelines [4, 7, 8] and a plethora of research in the field of optimising HDP management, there have been limited published studies describing the experiences of pregnant women with the management of HDP, as distinct from medication treatment.

A survey of women with pre-eclampsia or their partners, friends or relatives found that many had no knowledge of pre-eclampsia prior to diagnosis and once diagnosed, did not appreciate how serious or life threatening it was [9]. Women wanted access to information about pre-eclampsia and their experience contributed substantial anxiety towards future pregnancies. Partners/friends/relatives also had no prior understanding of pre-eclampsia and expressed fear for the woman and/or her baby [9]. A qualitative study of pregnant Moroccan women in the Netherlands or Morocco found that knowledge of symptoms related to hypertensive disorders of pregnancy was limited or absent [10]. The limited knowledge of hypertension-related symptoms and complications was based on their own experiences or on those of some family members or stories from their social network or internet, with little or no information on symptoms from their midwives or obstetricians [10]. The experiences, perceptions and behaviours of pregnant women with regard to the management of HDP during pregnancy remain largely unexplored. Understanding these perceptions and experiences is imperative to the optimisation of HDP management.

Aim

To explore pregnant women's perspectives of and experiences with clinical management of HDP.

Methods

Study design

A qualitative study using in-depth interviews was conducted, with pregnant women in their second or third trimester, recruited from antenatal clinics in two large tertiary hospitals in Melbourne, Australia.

Participants were sourced via a larger mixed-methods study, which included 100 pregnant women with HDP. Eligible participants were identified by one researcher (AH), who reviewed the medical records of pregnant women attending antenatal clinics, and then approached them individually. Participants were provided with written information for the larger study and on receipt of written informed consent, a questionnaire was given for self-completion. At the end of the questionnaire, participants were asked to indicate their interest in undertaking an interview. Of the 98 women who responded to the questionnaire, 65 expressed interest in being interviewed. Combined convenience and purposive sampling was conducted among these 65 women to seek a breadth of views. All of the women who were invited accepted to participate in an interview. Informed written consent was obtained prior to each interview, which included permission to audio record the conversation and to use quotations when anonymously reporting and publishing the results.

Study sample

Face-to-face, qualitative in-depth interviews were conducted with 27 pregnant women who were diagnosed with HDP and had a prescription for an antihypertensive medication, in either the second or third trimester of pregnancy, recruited from the antenatal outpatient clinics of two large tertiary maternity hospitals in Melbourne, Australia. Together, these hospitals provide antenatal care to approximately 13,000 women annually. They were identified using hospital records and approached during subsequent clinic visits. Participation was voluntary and involved informed consent.

The study sample size was determined based on theme saturation during analysis and was not predetermined. Recruitment ceased when no new information was forthcoming from the last three interviews, with regard to replication of data relating to attitudes towards HDP monitoring, perceptions of the development and management of complications (including early delivery) and perceptions of the women who had chronic hypertension.

Data collection

Interviews were conducted face to face by a single researcher (AH) a female Pharmacist (who was a PhD candidate at the time) after receiving training in in-depth interviewing prior to the commencement of the study using an interview guide developed based on the literature [11, 12] and was agreed upon by the authors (Table 1). Open-ended questions, such as "Tell me about …? ", followed by appropriate prompts, such as "How did that make you feel?" or "Can you explain that in more detail?" were used to guide the interview and encourage the interviewee to speak freely and in-depth about their experiences and thoughts. As the interviewer had met the participants during the larger study, some rapport had been established prior to the interview. The interviewer did not disclose their healthcare background to participants to avoid requests for health advice during the interviews. Interviews on average lasted 35 min (range 16 to 54 min) and were conducted in a private room near the antenatal clinics. No repeat interviews were performed.

Socio-demographic and self-reported health information was collected from participants through the questionnaire. Health information was verified, with consent, through medical records.

All interviews were audio-recorded, transcribed verbatim and de-identified. Interviews continued until data saturation was reached, deemed to be the point after

Table 1 Interview Topic Guide

Topic one: Understanding of hypertension
Explore the women's health beliefs surrounding their diagnosis of hypertension, e.g. when it was diagnosed and how they felt about it. Exploration into their beliefs regarding causation may also occur.
Topic two: Antihypertensive medication use during pregnancy
Explore concerns and experiences associated with the safety of using specific antihypertensive medications during pregnancy and thoughts on the importance of continuing them through pregnancy. Investigate whether there was decreased or increased use of any particular medication and why, and factors contributing to compliance. Ask participants to compare the use of blood pressure medications to other medications during pregnancy.
Topic three: Medication beliefs
Explore the women's general medication beliefs related to the use of other medications during the current pregnancy, including over-the-counter medications, vitamins and alternative therapies, their perceived safety and benefits.

which no new information for analysis was forthcoming [13]. The transcripts were not returned to the participants for comments or correction.

Data analysis

Data analysis occurred concurrently with the interviews. Initial coding was completed by AH using the qualitative data management software QSR NVivo 10 (QSR International) [14]. Inductive codes were generated systematically for the entire data set. Line-by-line analysis was then performed and nodes were created within NVivo. To ensure reliability, a random selection of 20% of the transcripts were coded independently by another member of the research team (KS). KS and KR read all the transcripts and any differences were discussed among all three to reach consensus. The researchers were all pharmacists; KS and KR had extensive experience in conducting qualitative research. Transcripts were reread by AH and KS to ensure that coding was accurate and all relevant data were included.

Thematic analysis was employed [15]. This was done across all HDP subtypes and severities to obtain a wide range of views. AH read and reread the codes, collapsed them into potential themes, compared the developing themes with the intact transcripts and cross referenced to HDP subtypes. When a pattern was seen within a certain subtype, coding was grouped specifically for that subgroup. Codes were arranged into potential themes. Themes were reviewed, refined and prepared into a final set with KS; sub-themes were identified within this process.

Results

Participants

Of the 98 women who responded to the questionnaire, 65 expressed interest in being interviewed. A combination of convenience and purposive sampling was conducted among these women to seek a wide breadth of views. All participants had a diagnosis of HDP and were prescribed antihypertensive medication. Interviews occurred during pregnancy except for one, which happened 1 day postpartum. All participants were aged 18 years or over and were fluent in English. Twenty-seven women were interviewed to reach data saturation. Their demographics, clinical and obstetric characteristics are shown in Table 2. Family members were present for some interviews but none of them participated in the interview or made comments. Field notes were taken by the interviewer during the interviews. No participants dropped out of the study or refused participation.

Eight participants were primigravidae, the remainder were multigravidae, including six who had previous miscarriages. One participant had an assisted pregnancy (in

Table 2 Demographics, clinical and obstetric characteristics ($n = 27$)

Characteristics	N
Country of birth	
Australia	18
Other (India, Philippines, Nigeria, Malaysia, Indonesia, United Kingdom)	9
Other health conditions	
None	16
Kidney disease	4
Depression	3
Type 2 diabetes	1
Congenital heart disease	1
Carpal tunnel syndrome	1
Rheumatoid arthritis	1
Gestational stage at interview	
Second trimester	6
Third trimester (32–34 weeks)	5
Third trimester (35–37 weeks)	6
Third trimester (≥37 weeks)	9
1 day postpartum	1
Time of hypertension diagnosis	
Pre-pregnancy	18
Current antihypertensive regimen started during pregnancy	9
< 20 weeks	3
At 20 weeks	0
> 20 weeks	6
Subtype of hypertension[a]	
Gestational hypertension	3
Pre-eclampsia	3
Severe pre-eclampsia	2
Chronic hypertension	10
Secondary hypertension	3
Pre-eclampsia superimposed on chronic hypertension	4
Severe pre-eclampsia superimposed on chronic hypertension	1
Pre-eclampsia superimposed on secondary hypertension	1
Severity of hypertensive disease[a]	
Mild-moderate	20
Severe	7
Antihypertensive medication[b]	
Methyldopa	11
Labetalol	15
Atenolol	2
Nifedipine	1
Oxprenolol	1
Phenoxybenzamine	1

[a] Classification according to the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guidelines 2014 [1]

[b] some participants were prescribed more than one antihypertensive medication

vitro fertilisation). Twelve were prescribed aspirin for the prevention of pre-eclampsia. Participants ranged in age from 26 to 42 years. The annotations at the end of each quote give a description of the participant's age, parity, gestational trimester and subtype of HDP at the time of the interview. The participants did not provide feedback on the findings.

Interview themes

Three major descriptive themes were discerned regarding the women's experiences with the management of HDP:

- attitudes towards monitoring of hypertensive disorders of pregnancy;
- attitudes and perceptions towards development and management of complications; and
- perceptions of pregnant women with chronic hypertension.

Theme 1: Attitudes towards monitoring of hypertensive disorders of pregnancy.

Most women had general trust in the hospital system. Some felt extra confidence knowing that they were being managed at a maternity hospital:

> *"Hospital is for saving lives of people...as soon as I see the hospital I know that I am in safe hands." (#14, 40 years, 2nd pregnancy, second trimester, severe pre-eclampsia).*

> *"I felt very comfortable here...it seems like they are well prepared for these things...I was in the section of the hospital where all women were in the same [hypertension] situation." (#9, 30 years, 1st pregnancy, second trimester, chronic hypertension).*

One woman expressed some distrust in general hospitals, which she perceived as not managing her BP well:

> *"My own GP at that time increased it [methyldopa] to six a day … the hospital … increased to 10 a day … but I couldn't lift my head up … so I ended up coming to the women's hospital to Emergency, because I felt like no one's helping me." (# 71, 37 years, 3rd pregnancy, third trimester, severe pre-eclampsia superimposed on chronic hypertension).*

Self-monitoring of BP was often recommended to women treated with antihypertensives. For some, it gave reassurance, but for others it was a source of confusion, with different messages coming from various members of the treating team:

> *"I take up to eight [methyldopa tablets] a day...I take two and then I'll see what my readings are...at home, myself...I also do it if I have any other symptoms....." (# 71, 37 years old, 3rd pregnancy, third trimester, severe pre-eclampsia superimposed on chronic hypertension).*

> *"One of the physicians I saw told me to do it three times a day … three times in a row and then she said take the average of the second two readings each time...Then I told the obstetrician my readings and she said the machine that I had at home is undermeasuring...but...the physician, he was quite interested...he wanted to see my readings because he likes to compare his machine to home machines." (#53, 40 years, 6th pregnancy, third trimester, secondary chronic hypertension).*

Some women had milder HDP in previous pregnancies, which gave them a sense that the monitoring and management was overstated. Others with more severe cases and their prior experience brought back memories initiating action to make plans:

> *"With [child 1] it was really bad during pregnancy. With [child 2] it was bad just in the last couple of weeks and straight afterwards...[child 3] was bad, but not really bad enough. They just called it hypertension, pregnancy induced hypertension and they just left it at that. They didn't make a big song and dance about it...They made a big song and dance last time [child 4] and then this time [they said] 'You're going for your monitoring'...come back a week later...'You're going for your monitoring,' couple of hours later – 'You're being admitted'...Then a couple of hours later...'You're starting on medicine." (#6, 28 years, 4th pregnancy, 1 day postpartum, gestational hypertension).*

> *"Last Wednesday when they [found] blood pressure's up … it just brought back memories from last time because same thing. I just went in for an appointment and I never came home...Ten days later I came home with a baby. So I think those aspects freak me out a bit because it's like 'Oh, it's happening again' … every appointment...even this appointment, we've got contingency plans, just in case." (#74, 36 years, 2nd pregnancy, third trimester, chronic hypertension).*

Some women wondered about why they were not told their BP readings unless they asked:

> *"I find it funny that when they take your blood pressure they don't tell it to you. I always have to ask, always, no matter who it is, midwife, physician, obstetrician. They take it and they walk away. It's my body but they don't tell me." (#53, 40 years, 6th preg-*

nancy, third trimester, secondary chronic hypertension).

Close monitoring was perceived as frustrating, but also as part of the life adjustments that come with having a baby. Some women considered spending four hours in the day assessment centre for monitoring their BP better than being an inpatient and staying overnight, whilst others saw it as an annoyance:

"I am happy to come back every day as long as I don't have to spend overnight here. I am happy to be here for 12 hours a day, but I just can't be away from my children at night time." (#29, 26 years, 3rd pregnancy, second trimester, secondary chronic hypertension).

"They just monitor me at that perinatal care...you just sit here four hours a day...it's shocking...worse than taking the tablet." (#90, 35 years, 7th pregnancy, third trimester, chronic hypertension).

"The only thing that was slightly frustrating was [that] four hours is a long time to sit around, but again, you're having a baby so you've got to make a few adjustments to your life." (#99, 34 years, 1st pregnancy, third trimester, pre-eclampsia).

Some of the women required a short inpatient stay to stabilise their BP and avert an emergency premature delivery. For many, it was an emotional experience filled with apprehension and uncertainty about the future:

"It was very emotional, very scary, and at the same time still trying to stay strong. So that when my husband and my kids came in, I was like 'I've just got a little bit high blood pressure, everything's alright'...I didn't know that a possible side effect of having the blood pressure is that they may have to deliver the baby [early]." (#32, 42 years, 3rd pregnancy, third trimester, severe early onset pre-eclampsia).

"B.P. at first was around 160...she came back 15 minutes – 170, another 15 minutes 180, within 10 minutes 190...I got nervous … After 160 they gave me ...labetalol...but [the BP] did not go down... There were other tablets they gave to me but [the BP still] didn't go down...All the doctors came up...surrounded with those with scrub suits, I panic...blood pressure...went to 210..they were panicked...one just looked at me and said "AAAH". I cried...of course you feel anxious, you feel sad...worried... what's going on with me? I cried and cried. It was just like a movie, they push my bed out from the room and sent me quickly down to the birthing suite [in case delivery was imminent]." (#14, 40 years, 2nd pregnancy, second trimester, severe pre-eclampsia).

Theme 2: Attitudes and perceptions towards development and management of complications.

For many women, the diagnosis of pre-eclampsia came as a shock. Those with prior experience knew what to expect and were hesitant to cease antihypertensive treatment even if their BP was low. One woman without prior experience self-educated about pre-eclampsia, became concerned about the symptoms and developed anxiety about developing it:

"It was a shock and it was a bit scary...I thought 'I've heard of pre-eclampsia but I don't really know what it is'...but all the staff, they explained everything quite well... [I could see] how they were being very concerned about it, so that was making me realise this isn't just a small thing, this is obviously a serious situation." (#32, 42 years, 3rd pregnancy, third trimester, severe early onset pre-eclampsia).

"I didn't want to stop the medication altogether, only because I just didn't want to go through the path of having the high blood pressure affect the baby [intrauterine growth restriction]." (#8, 36 years, 2nd pregnancy, third trimester, chronic hypertension).

"I was reading that if you do develop pre-eclampsia... it is a risk for the baby and the mother as well. Upon reading all that information...I became a bit paranoid, swollen foot, swollen hands, they're part of the symptoms, headaches, generally not feeling well...I became quite paranoid looking at my symptoms and [thinking] have I got this, have I not got this? But the doctors actually did say that I have got borderline pre-eclampsia, so they were waiting to see if I was going to develop it. However, they haven't been able to reassure me that I'm not going to develop it and...that was quite scary for me." (# 24, 35 years, 1st pregnancy, third trimester, chronic hypertension diagnosed during pregnancy).

Some women understood that low-dose aspirin was being used for prevention of pre-eclampsia, whereas others did not always perceive it as being effective for this purpose. Many women thought that aspirin helped with controlling the BP rather than for prevention of pre-eclampsia:

"I started on aspirin throughout the pregnancy … just to...prevent mild pre-eclampsia happening again." (#64, 30 years, 3rd pregnancy, third trimester, chronic hypertension).

"Obstetrician put me on one aspirin a day which is supposed to help control blood pressure. So perhaps that's also why my blood pressure is being well controlled." (#21, 35 years, 1st pregnancy, second trimester, chronic hypertension).

Most women had a general understanding that the only way to stop the direct effects of pre-eclampsia was to deliver the baby for the safety of both mother and child. The level of comfort with such a decision varied depending on the gestational stage of diagnosis of pre-eclampsia:

"I was really disappointed and very worried about the effect it [pre-eclampsia] would have on the baby [at 21 weeks] and whether or not I would be able to carry the baby to a safe week. I just thought...if something had happened and I was forced, like accidentally went into labour too early or something like that, the baby's chances of survival would be very low and I was really upset." (#21, 35 years, 1st pregnancy, second trimester, chronic hypertension).

"All I know is that you just need to get the baby out...I mean plenty of women and plenty of babies survive it...but you need to detect it pretty quickly before it turns into the full...is it eclampsia?" (#41, 34 years, 1st pregnancy, third trimester, chronic hypertension).

Although many women understood that they would not continue to full-term, their perceptions and fears about the potential for a premature delivery were related to their week of gestation, concern about the welfare of the baby, and fear of separation after the birth:

"I know from my reading that 24 weeks, it's still not ideal obviously, but if you had the baby at 24 weeks that the chance of survival was higher. I think it was 43% chance of survival from this...prior to that it was like 16% chance of survival...My sister-in–law, who is a midwife, had said...they consider 26 weeks more viable. So after that it was like, right (a) to get to 24, (b) get to 26." (#21, 35 years, 1st pregnancy, second trimester, chronic hypertension).

"I am just worried about my baby [having] to be delivered earlier because you see the consequences... you see things happen in the future...they are still very weak...no sucking reflex yet, the lungs are not fully developed, so many things not developed...she may live but maybe there are some disabilities...I am just hoping that I will reach even up to 30 weeks or 32 weeks. That would make me feel better." (#14, 40 years, 2nd pregnancy, second trimester, severe pre-eclampsia).

"I was 28 weeks [when I developed severe pre-eclampsia]...they gave me steroid injections to increase the lung capacity of the baby...One of the doctors came from the NICU with a leaflet about possibly having a premature baby...that was very upsetting...and to think of having the baby...then me going home with the baby staying here is just a very scary thought."(#32, 42 years, 3rd pregnancy, third trimester, severe early onset pre-eclampsia).

Intervention with the delivery process was a likely reality for many women who had a prospect of early delivery. Some women were apprehensive about the prospect of induction of labour or caesarean section but understood that it was for their benefit and that of their child. Others were hesitant to allow for intervention unless the risks were made clear:

"So a little bit scary, but in a way I want it to, because I'm starting to feel the uncomfortable risk that's associated with pregnancy in this condition. Knowing that she's at full term now at 37 weeks and she's fine and healthy, I don't want to develop pre-eclampsia if I can help it." (# 24, 35 years, 1st pregnancy, third trimester, chronic hypertension diagnosed during pregnancy).

"I'm trying to push it off because I don't want to do it. I like to have the baby when the baby's ready, not when they tell me to. But if they tell me to because it's really dangerous for me then I'll listen to them obviously …." (#53, 40 years, 6th pregnancy, third trimester, secondary chronic hypertension).

Concerns about lack of information sharing by health professionals led some women to feel that they were left out of the planning for potential intervention in the delivery, whilst others voiced concern about having low-dose aspirin in the context of a possible emergency caesarean section:

"I even asked her last time actually because she said...I'm happy with the baby's growth, but the blood pressure's going up so … she said 'I'm formulating a plan in my mind' but she doesn't like to disclose it. I don't know why. It's about me; I don't know why she just doesn't tell me." (#53, 40 years, 6th pregnancy, third trimester, secondary chronic hypertension).

"I also thought...what if I have an emergency caesarean tomorrow and I haven't gotten off the aspirin? Is it going to cause me issues?" (#29, 26 years, 3rd pregnancy, second trimester, secondary chronic hypertension).

Theme 3: Perceptions of pregnant women with chronic hypertension.

Many women with chronic hypertension were already on antihypertensive medication not deemed safe during pregnancy when they found out they were pregnant. For some, it was changed to a safer alternative as soon as possible, whilst for others, the decision to change the medication was delayed and the patient's assessment of potential risks was downplayed:

> *"I was on medication [telmisartan]...then when I had the kidney scan and I found out [that I was pregnant], my G.P. said 'You've got to stop taking that medication because it's not safe...so then she gave me another one to take." (#2, 30 years, 1st pregnancy, third trimester, secondary chronic hypertension).*

> *"The first time I found out I was pregnant I went to a GP...I told the GP that I'm taking atenolol, and then she told me that...atenolol is not recommended for pregnancy... so I asked....What medication do you think that I should take?'...she said she doesn't dare to prescribe me any medicine because she knows she is going to refer me to a hospital." (#59, 34 years, 1st pregnancy, second trimester, chronic hypertension).*

Other women had their antihypertensive changed during the pre-pregnancy planning stage:

> *"[To be safe during pregnancy] I would just have to change my medications. The medication I was on I couldn't be on while being pregnant. So when we decided to try for our first child, I went on the Aldomet and oxprenolol and that's what I pretty much stayed on because we always wanted a second child." (#1, 39 years, 2nd pregnancy, third trimester, secondary chronic hypertension).*

Some women with chronic hypertension had concerns about lack of information sharing by health professionals and felt that they were not well informed of the potential risks that their hypertension may have on the pregnancy. Some mentioned that they may have 'taken it more seriously' if they had known about the risk of premature delivery associated with uncontrolled hypertension, whilst others had some limited awareness of pre-eclampsia:

> *"When they told me I had protein in my urine, I was a bit scared because I don't know if it's related to my BP." (#4, 33 years, 1st pregnancy, third trimester, chronic hypertension).*

One woman was very anxious about her diagnosis of severe, early-onset pre-eclampsia so she did some 'self-research'. Unfortunately, she misinterpreted the information and caused herself extra unwarranted fear:

> *"I read on [US website found on Google] and found that 80% die after/during birth that have pre-eclampsia. That was really scary." (#71, 37 years, 2nd pregnancy, third trimester, severe pre-eclampsia superimposed on chronic hypertension).*

The information on the US Preeclampsia Foundation website actually states that "Nearly 80% of women who die from pre-eclampsia die post-partum" [16].

For some women with chronic hypertension, lack of knowledge of the seriousness of the condition resulted in lack of comprehension of the importance of BP monitoring and treatment:

> *"I think it was about 140 over 110 or something like that … which is pretty normal for me but they think it's high … I feel alright. It's all good." (#90, 35 years, 7th pregnancy, third trimester, chronic hypertension).*

> *"I really tried for weeks not to go on [the antihypertensive], but then when she said that maybe you could have a stroke, I got a bit scared, a lot scared … I got really worried because then they said … you could have problems, the baby could die. And I got really upset when she said the baby could not get enough oxygen. I just felt, oh just have whatever it is." (#22, 37 years, 3rd pregnancy, third trimester, chronic hypertension).*

Most women who had chronic hypertension were under a model of care involving both an obstetrician and a physician. One was triaged to midwife-only care, despite having a diagnosis of chronic hypertension and being prescribed an antihypertensive medication. This then caused a delay in the change of the antihypertensive to a safer alternative:

> *"Actually, I asked the midwife whether it [atenolol] is safe or not [at 18 weeks gestation]...and then she said that...it should be okay, but to be safe discuss with the physician. And so, because she said it should be okay, I presumed that 'Oh that is okay'...but then the physician said 'No, it's better not to...so from now onwards you have to take this medicine [oxprenolol]." (#59, 34 years, 1st pregnancy, second trimester, chronic hypertension).*

Many women had their first antenatal appointment at the hospital between 16 and 20 weeks gestation. Some women, especially those with chronic hypertension, had concerns about the timing of this appointment:

"It takes a long time now for women to get their first appointment through the hospital. It wasn't like that, I think, about 10 years ago, must've changed by now … Now you have to wait 'til you're about 18, 20 weeks before you get your first actual appointment...and if you've got other health issues, things can go wrong, which it did with me." (#71, 37 years, 2nd pregnancy, third trimester, severe pre-eclampsia superimposed on chronic hypertension).

Some women did not know that they had high BP before pregnancy. This may have been because they did not get regular check-ups with the GP or that their BP was not routinely checked at regular GP visits:

"I think if I had never gotten pregnant, I definitely would not have had [high BP], would not have to be on medication … because I wouldn't be under the strain that I am. And also I wouldn't be in with the doctor. I don't think I would've gone to the doctor and said put me on medication … because I didn't, want anything to change. But my lifestyle is changing now so I don't have a choice." (#18, 35 years, 2nd pregnancy, second trimester, chronic hypertension).

"It [BP] was quite normal before the pregnancy, so obviously it's pregnancy-related according to the doctors [despite having been diagnosed at 7 weeks]." (#24, 35 years, 1st pregnancy, third trimester, chronic hypertension diagnosed during pregnancy).

Many women had developed chronic hypertension after a previous pregnancy that involved either gestational hypertension or pre-eclampsia. Some of them had routine follow-up for their hypertension postpartum and understood that it was now chronic hypertension, whilst others did not:

"Once I'd had the baby they changed my medication to the perindopril...I was then checking my BP at home...the readings were fine...when they did get too high, I'd go back to my local GP who would then once again adjust the dosage accordingly...I have been told by my local GP that generally once you're on a blood pressure medication, you're on it for life, whether it's a minimal dosage or, depending on what the readings are, what they need to give...I'm happy to stay on that." (#8, 36 years, 2nd pregnancy, third trimester, chronic hypertension).

"I got increased blood pressure at the end [of the previous pregnancy] and they put me in perinatal care, but then afterwards it was okay....I honestly just didn't go to the doctor, and I haven't gone to the doctor since I fell pregnant with this one." (#90, 35 years, 7th pregnancy, third trimester, chronic hypertension).

One woman described having been prescribed an antihypertensive during her previous pregnancy and never told to stop it, so she continued with no formal review of her hypertension until the current pregnancy:

"They never told me to stop taking the tablet [labetalol] after I had him [first child] so I just kept continuing with it...I saw the physician [during this current pregnancy] and he just said just keep taking it...he actually questioned 'Did they ask you to stop it?...I said no one spoke to me about anything...I was here for a week after I had him [first child]...no one ever discussed it." (#58, 38 years, 2nd pregnancy, third trimester, chronic hypertension).

Discussion

Trust in the hospital system, positive attitudes towards close BP monitoring as well as self-monitoring of BP (SMBP) and a realistic approach to emergency antenatal hospital admissions contributed to a positive attitude towards monitoring of HDP. Most of the women in our study had a general trust in the healthcare system. Distrust surfaced when health services outside the women's hospital were not seen as able to control hypertension early in the pregnancy, triggering patient-initiated referral to the women's hospital. Trust of healthcare systems in western countries is generally declining [17]. It is, however, important to note that pregnant women with HDP are considered to be in a high-risk pregnancy and are thus more vulnerable than the general population. Therein lies dependence on the hospital system, especially in urgent situations such as needing to lower BP or planning for an early delivery, similar to the dependence reported in patients with coronary heart disease [18].

Anecdotally, it is common for healthcare professionals to mention that the BP reading is 'good' or 'too high' without telling the patient the systolic/diastolic numbers. An important factor relating to patient evaluation of care is their involvement in decision-making [19]. Most of the women in our study were not involved in decision-making, leaving some to wonder why this was so. This suggests that pregnant women with HDP would like to be better informed of their situation and be part of the decision-making process when deemed appropriate. This is consistent with the women's views from the pilot of the CHIPS study who enjoyed being heavily involved in their BP management [20]. One way to have women more involved in their BP management is to encourage SMBP. SMBP in the general population has been shown to reduce BP [21] and improve adherence

to antihypertensive medication [22]. In our study, SMBP was often recommended to women who were prescribed antihypertensive medications. This was taken up well by most, similar to the CHIPS pilot study [20]. SMBP during pregnancy has also been shown to be reassuring and not anxiety provoking [23] which was seen in our study. A recent survey of 5555 pregnant women from antenatal clinics in 16 hospitals in England, found that nearly half of the 389 hypertensive women reported SMBP, and that the majority of them (79%) shared their BP readings with their treating doctor [24]. Such partnership has been shown to improve patient adherence in the general population [25]. There is however an assumption that because these women are in a high-risk pregnancy, the healthcare professionals (HCP) tend to take over and do not acknowledge that the women are quite competent and that with the correct information can be involved in SMBP in collaboration with the HCPs. It is thus important to have a good doctor-patient relationship to reduce confusion, instil confidence in SMBP and complete the circle of care.

Those with prior experience with HDP and monitoring had varied views, often depending on the severity of disease in the previous pregnancy (ies). Good communication about how HDP can vary from one pregnancy to another, being either worse or better, may assist in reducing the cynicism of some and reassure others. Similarly, those who had prior experience with pre-eclampsia were a lot more confident in their management and knew what to expect. Those who did not have prior experience were often in shock and were at times anxious about the diagnosis, a finding similar to another study relating to the understanding of pre-eclampsia [26]. Moreover, the use of low-dose aspirin to prevent pre-eclampsia was only partially understood by women in our study. This indication should be communicated clearly to women who are at high risk of developing pre-eclampsia. The plan for the cessation of aspirin before delivery should also be communicated clearly to reduce any anxiety that may be present, especially in terms of a potential emergency delivery.

At times, antenatal inpatient admission was required to stabilise BP and closely monitor both the mother and baby. This was a particularly apprehensive time, especially for women who had not experienced HDP during a previous pregnancy. It is important to have good, clear communication with women about the need for close monitoring, affirmation concerning their status as worthy of hospital care, provision of consistent information, inclusion in decision-making and good social support [27]. A possible alternative to inpatient admission can be pregnancy day assessment monitoring. Despite limited research into this model of care, pregnant women have been found to prefer a four-hour stay rather be admitted to hospital for one or more nights, if the situation is deemed safe to do so [3]. This is consistent with our findings. Once again, clear consistent information regarding the need for this type of monitoring should be given to women who require it. Recent advancements in the integration of telemedicine into antenatal care [28] have encouraged early research into the feasibility of incorporating this for women with HDP to reduce the burden of multiple antenatal hospital visits [29]. The unpredictable course of worsening BP and the development of pre-eclampsia pose specific challenges to this monitoring and would require a holistic approach. A recent single centre study in the UK [29] developed and trialled an innovative SMBP intervention including a downloadable mobile app in for women with HDP to monitor for signs of pre-eclampsia or worsening hypertension. Although this study showed positive acceptance and compliance from the women, further research is required to meet the standard of care required for them [29].

In general, most women desire to labour spontaneously and have a natural birth [30]. When the reality that the only way to stop the direct effects of pre-eclampsia is to deliver the baby at any given gestational week is revealed to some women, it is received with disappointment. Good communication by the treating doctor about the intention to preserve the pregnancy for as close as possible to term is required. Likewise, sound communication about the need for a premature delivery should be communicated clearly. Moreover, it has been shown that pregnant women who require induction of labour or caesarean section often feel left out of the decision-making process [30]. An Australian study of women's experiences of decision-making and attitudes in relation to induction of labour, reported a clear need for women to be provided with more information and agency when making decisions about their timing of birth, particularly when there are multiple reasonable treatment options [30]. Furthermore, emergency caesarean sections have been found to negatively contribute to several psychosocial outcomes for women, in particular post-traumatic stress [31]. There is, thus, a need for careful consideration and counselling for women after an emergency caesarean delivery. This can involve the members of the antenatal treating team but also counsellors or psychologists. Moreover, counselling of pregnant women who are at risk of emergency caesarean, either because of their HDP or otherwise, about this possibility may help to pre-empt potential trauma.

Research into the management experiences of pregnant women with chronic hypertension, as distinct from medication treatment, is scant. Our study has highlighted the need for extra attention to be given to improve

management pre-conception, during the pregnancy and postpartum. A qualitative study exploring knowledge and attitudes related to pregnancy and preconception health in women with chronic medical conditions, including chronic hypertension, found that the women had limited knowledge of the specific potential complications of pregnancy [32]. Some women in our study also displayed limited understanding of the potential risks that they may endure during pregnancy and thus had a lack of comprehension of the seriousness of the condition. Counselling women pre-conception regarding potential risks during pregnancy allows them to be more aware of what to expect [33]. Moreover, an open conversation about the information that the pregnant woman may have either from prior experience or 'self-research' would help to improve understanding as well as avoiding confusion and unnecessary anxiety. The provision of written material so that the women can refer to it when necessary would also be appropriate. Another facet of management of chronic hypertension pre-conception is the initial diagnosis of hypertension. Some women in our study were not aware of their BP readings before pregnancy and were diagnosed with hypertension quite early in pregnancy and thus classed as having chronic hypertension. Regular checking of BP in women of reproductive age at routine GP visits may help to identify chronic hypertension earlier. This can help in the planning of a pregnancy, or ensure that the BP is under control in the case of an unexpected pregnancy. Similarly, for those who have chronic hypertension and are prescribed antihypertensives, switching the medication to one that is safer during pregnancy, either pre-conception or as early as possible, can help to reduce fetal exposure and reduce the mother's anxiety. Both GPs and community pharmacists have a role in counselling women of reproductive age who are prescribed an antihypertensive. A simple question as to whether the women is planning a pregnancy can help initiate the necessary conversation and trigger the switch to a safer alternative in a timely manner. Various resources are available to help make the decision to change the antihypertensive, including drug information lines at maternity hospitals. Moreover, a large number of women who had entered our study with chronic hypertension had developed the condition after a previous pregnancy that was affected by gestational hypertension or pre-eclampsia. Furthermore, our study found that many women developed chronic hypertension soon after a pregnancy complicated by HDP. This is supported by a recent systematic review and meta-analysis which reported that the risk of developing hypertension after HDP is highest in the early postpartum period [34]. The authors also suggested that diagnosis and targeted interventions to improve maternal cardiovascular health may need to be commenced in the immediate postpartum period [33]. We agree with this and call for a more integrated follow up with women in the postpartum period and beyond. This may involve the GP and the community pharmacist for easy accessibility for the women.

Although most women with chronic hypertension in our study were under a model of care involving an obstetrician and a physician, one was under midwifery care despite having chronic hypertension and being prescribed an antihypertensive. Although it is recognised by Australian guidelines for the management of HDP that midwives play a role in a multidisciplinary team in relation to management of HDP [4, 35], they are not qualified to independently prescribe medication and manage cases of pregnant women with chronic hypertension requiring treatment. Similarly, a recent scoping review found that practising midwives worldwide lack knowledge on several aspects of pre-eclampsia diagnosis and care and have called for an increase in in-service training to increase midwives' knowledge in this area [36]. It is therefore important that all pregnant women who have chronic hypertension be under the doctor model of care to monitor both mother and baby throughout the pregnancy.

Recommendations for practice

Good communication between the HCP and the patient is important to optimise management. Clear, direct and concise information about various facets of the management of HDP should be provided for all women who experience HDP.

Women who experience any form of HDP during pregnancy should be invited to be part of the decision-making pertaining to the monitoring of BP and progression to pre-eclampsia as well as the timing and mode of delivery when appropriate.

There should be a priority for women with chronic hypertension to be seen at the hospital under an obstetrician led model of care before 18 weeks, not only for the regular monitoring of BP and fetal progress but also for the timely prescription of low-dose aspirin before 16 weeks gestation for the prevention of pre-eclampsia. Furthermore, other health professionals, including psychologists and pharmacists, can be involved in the prenatal care of these women to address potential fear and anxiety as well as the optimal use of medication.

Women who have chronic hypertension and are of reproductive age should be informed of the potential risks of pregnancy and be switched to a pregnancy safe antihypertensive in the preconception stage.

Women who experience gestational hypertension or pre-eclampsia during pregnancy should have their BP monitored postpartum by the GP or the community

pharmacist to identify any risk of developing severe cardiovascular events.

Recommendations for future research

Currently, much of the monitoring of HDP requires a hospital visit. Further research into the feasibility of telehealth for the monitoring of HDP, especially in mild cases will help to include patients in the decision-making. Moreover, future research into the role of the GP and the community pharmacist in the pre-pregnancy planning stage for those with chronic hypertension and postpartum for those with gestational hypertension or pre-eclampsia is warranted.

Strengths and limitations

This qualitative study is the first to use in-depth interviews to explore pregnant women's experiences, perceptions and behaviours with regard to the management of HDP during pregnancy. Our study included women with all forms of HDP except HELLP and eclampsia, as the interviews were done when the women were in a comfortable, non-emergency situation. Participants varied in gestation stage, subtype of HDP, severity of HDP, ethnicity and socioeconomic status allowing for a wide range of views. The interviews were conducted during pregnancy thus reducing recall bias. This is in contrast to other qualitative studies which explored aspects of HDP in retrospect [27, 35, 37]. Recruitment was from two major public maternity referral hospitals in Melbourne with a widespread combined catchment including metropolitan, regional and rural areas. Participants did not include those in the first trimester of pregnancy, as most were scheduled to attend the antenatal clinics after 12 weeks gestation. Views of women with chronic hypertension during the first trimester of pregnancy may vary from those in the second and third trimesters and they were not captured. Women with poor English skills were excluded from the study, therefore, caution should be taken in the extrapolation of our findings to women from non-English speaking backgrounds.

Conclusions

The clinical management experiences of pregnant women with HDP were varied. Many women did not feel that they were well informed of treatment and management decisions and had a desire to be more informed and more involved in decision-making. Clear, concise information about various facets of HDP management including BP monitoring, administration of low dose aspirin in women with a high risk of developing pre-eclampsia, prescription of the appropriate antihypertensive, and planning for potential early delivery are required. In addition, cardiovascular pre-pregnancy planning and postpartum follow-up should be routinely offered to women.

Acknowledgements
We would like to thank the staff at both the Mercy Hospital for Women and the Royal Women's Hospital for their help with this study. We would also like to thank all the women who participated.

Authors' contributions
All authors contributed to the conception and design of the study. Patient recruitment and in-depth interviews were undertaken by AH. Data analyses and interpretation were performed by AH, KS and KR. The manuscript was written by AH and critically reviewed by all authors. All authors read and approved the final manuscript.

Funding
This study did not receive any funding.

Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available due to privacy surrounding participant information as stipulated in the written consent form, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from Mercy Health Human Research Ethics Committee Heidelberg-Melbourne (R12/62) 08/01/2013, The Royal Women's Hospital Research and Human Research Ethics Committee Parkville-Melbourne (R13/18) 12/07/2013 and Monash University Human Research Ethics Committee Clayton-Melbourne (CF13/117) 18/01/2013. Informed written consent was obtained prior to each interview, which included permission to audio record the conversation and use quotations when anonymously reporting and publishing the results. All methods were carried out in accordance with relevant guidelines and regulations of the ethics committees.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, Melbourne, Victoria, Australia. [2]Reading School of Pharmacy, University of Reading, Whiteknights, Reading RG6 6AP, UK.

Received: 12 July 2021 Accepted: 8 November 2021
Published online: 02 December 2021

References

1. Royal Australian and New Zealand College of Obstetrians and Gynaecologists. Maternity Care in Australia. 1st ed; 2017.
2. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. Am J Obstet Gynecol. 2017;216(2):110–20 e6.
3. Dunlop L, Umstad M, McGrath G, Reidy K, Brennecke S. Cost-effectiveness and patient satisfaction with pregnancy day care for hypertensive disorders of pregnancy. Aust NZ J Obstet Gyn. 2003;43(3):207–12.
4. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA, et al. The SOMANZ guidelines for the Management of Hypertensive Disorders of pregnancy 2014. Aust NZ J Obstet Gyn. 2015;55(1):11–6.

5. Koopmans CM, Bijlenga D, Groen H, Vijgen SMC, Aarnoudse JG, Bekedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet. 2009;374(9694):979–88.
6. Broekhuijsen K, van Baaren GJ, van Pampus MG. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): a multicentre, open-label randomised controlled trial (vol 385, pg 2492, 2015). Lancet. 2016;387(10021):848.
7. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive disorders of pregnancy ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018;72(1):24–43.
8. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P, Pr CHD. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens. 2014;4(2):105–45.
9. East C, Conway K, Pollock W, Frawley N, Brennecke S. Women's experiences of preeclampsia: Australian action on preeclampsia survey of women and their confidants. J Pregnancy. 2011. Article number 375653.
10. Ouasmani F, Engeltjes B, Haddou Rahou B, Belayachi O, Verhoeven C. Knowledge of hypertensive disorders in pregnancy of Moroccan women in Morocco and in the Netherlands: a qualitative interview study. BMC Pregnancy Childbirth. 2018;18(1):344.
11. Sawicki E, Stewart K, Wong S, Leung L, Paul E, George J. Medication use for chronic health conditions by pregnant women attending an Australian maternity hospital. Aust NZ J Obstet Gynaecol. 2011;51(4):333–8.
12. Lim AS, Stewart K, Abramson MJ, Ryan K, George J. Asthma during pregnancy: the experiences, concerns and views of pregnant women with asthma. J Asthma. 2012;49(5):474–9.
13. Fusch PI, Ness LR. Are we there yet? Data saturation in qualitative research. Qual Rep. 2015;20(9):1408–16.
14. Microsoft Windows NVivo 10. [Available from: http://help-nv10.qsrinternational.com/desktop/concepts/about_nodes.htm.] Accessed 21 Feb 2020.
15. Braun VC, V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77–101.
16. Preeclampsia Foundation 2021 [Available from: https://www.preeclampsia.org/health-information]. Accessed 11/02/2021.
17. Ward PR, Rokkas P, Cenko C, Pulvirenti M, Dean N, Carney S, et al. A qualitative study of patient (dis) trust in public and private hospitals: the importance of choice and pragmatic acceptance for trust considerations in South Australia. BMC Health Serv Res. 2015;15:297.
18. Meyer SB, Ward PR. Differentiating between trust and dependence of patients with coronary heart disease: furthering the sociology of trust. Health Risk Soc. 2013;15(3):279–93.
19. Hodnett ED. Pain and women's satisfaction with the experience of childbirth: a systematic review. Am J Obstet Gynecol. 2002;186(5):S160–S72.
20. Magee LA, von Dadelszen P, Chan S, Gafni A, Gruslin A, Helewa M, et al. Women's views of their experiences in the CHIPS (control of hypertension in pregnancy study) pilot trial. Hypertension Pregnancy. 2007;26(4):371–87.
21. Tucker KL, Sheppard JP, Stevens R, Bosworth HB, Bove A, Bray EP, et al. Self-monitoring of blood pressure in hypertension: a systematic review and individual patient data meta-analysis. PLoS Med. 2017;14(9):e1002389. https://doi.org/10.1371/journal.pmed.1002389.
22. Ogedegbe G, Schoenthaler A. A systematic review of the effects of home blood pressure monitoring on medication adherence. J Clin Hypertens (Greenwich). 2006;8(3):174–80.
23. Hinton L, Tucker KL, Greenfield SM, Hodgkinson JA, Mackillop L, McCourt C, et al. Blood pressure self-monitoring in pregnancy (BuMP) feasibility study; a qualitative analysis of women's experiences of self-monitoring. BMC Pregnancy Childbirth. 2017;17(1):427. https://doi.org/10.1186/s12884-017-1592-1.
24. Tucker KL, Hodgkinson J, Wilson HM, Crawford C, Stevens R, Lay-Flurrie S, et al. Current prevalence of self-monitoring of blood pressure during pregnancy: the BUMP survey. J Hypertens. 2021;39(5):994–1001.
25. Sabate E, editor. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
26. You WB, Wolf M, Bailey SC, Pandit AU, Waite KR, Sobel RM, et al. Factors associated with patient understanding of preeclampsia. Hypertens Pregnancy. 2012;31(3):341–9.
27. Barlow JHHJ. Thornton S Women's experiences of hospitalisation with hypertension during pregnancy: feeling a fraud. J Reprod Infant Psychol. 2008;26(3):157–67.
28. Zairina E, Abramson MJ, McDonald CF, Li J, Dharmasiri T, Stewart K, et al. Telehealth to improve asthma control in pregnancy: a randomized controlled trial. Respirology. 2016;21(5):867–74.
29. Sheehan EKA, Kay L. Using a smartphone app to identify signs of pre-eclampsia and/or worsening blood pressure. Br J Midwifery. 2019;27(2):92–9.
30. Coates D, Goodfellow A, Sinclair L. Induction of labour: experiences of care and decision-making of women and clinicians. Women Birth. 2020;33(1):e1–e14.
31. Benton M, Salter A, Tape N, Wilkinson C, Turnbull D. Women's psychosocial outcomes following an emergency caesarean section: a systematic literature review. BMC Pregnancy Childbirth. 2019;19(1):535.
32. Chuang CH, Velott DL, Weisman CS. Exploring knowledge and attitudes related to pregnancy and preconception health in women with chronic medical conditions. Matern Child Hlth J. 2010;14(5):713–9.
33. Seely EW, Ecker J. Chronic hypertension in pregnancy. Circulation. 2014;129(11):1254–61.
34. Giorgione V, Ridder A, Kalafat E, Khalil A, Thilaganathan B. Incidence of postpartum hypertension within 2 years of a pregnancy complicated by pre-eclampsia: a systematic review and meta-analysis. BJOG. 2021;128(3):495–503.
35. Roberts LM, Davis GK, Homer CS. Pregnancy with gestational hypertension or preeclampsia: a qualitative exploration of women's experiences. Midwifery. 2017;46:17–23.
36. Garti I, Gray M, Tan JY, Bromley A. Midwives' knowledge of pre-eclampsia management: a scoping review. Women Birth. 2021;34(1):87–104.
37. Shanmugalingam R, Mengesha Z, Notaras S, Liamputtong P, Fulcher I, Lee G, et al. Factors that influence adherence to aspirin therapy in the prevention of preeclampsia amongst high-risk pregnant women: a mixed method analysis. PLoS One. 2020;15(2):e0229622. https://doi.org/10.1371/journal.pone.0229622.

Publisher's Note

6.3 Discussion and Summary

The experiences of the women demonstrated gaps in clinical management from their point of view. This has not been previously reported in the literature. The lack of knowledge surrounding several facets of the management of hypertensive disorders of pregnancy led to apprehension in some and a lack of comprehension of the seriousness of their condition in others. All women with HDP should be given clear and concise information about various facets of HDP management. This allows the women to have a clearer understanding of their own situation and potentially be part of decision making, especially when there are multiple options. Women who have chronic hypertension and are of reproductive age are at higher risk of developing complications of HDP including pre-eclampsia, whether or not they are treated with antihypertensive medication. These women should be informed of the risks pre-pregnancy and should be routinely offered information regarding these possible complications and the need for close BP monitoring, possible antihypertensive treatment and low-dose aspirin, screening for pre-eclampsia and the possibility of early delivery. Moreover, women of reproductive age who have chronic hypertension and are being treated with antihypertensives should be advised to change the antihypertensive to a safer alternative when planning pregnancy. This conversation can be initiated by the GP or the community pharmacist. This is investigated further in the study reported in **Chapter 7**. Similarly, these women should be given priority to have their initial antenatal appointment between 10-12 weeks gestation and be managed by an obstetric model rather than a midwifery model alone to allow continuity of high-level care and monitoring of the HDP for the safety of both the mother and the baby.

CHAPTER 7

PROSPECTIVE COHORT STUDY OF THE MANAGEMENT OF HYPERTENSIVE DISORDERS OF PREGNANCY

7.1 Introduction

Unique patient perspectives on various aspects of management of HDP were expressed in the in-depth interviews described in **Chapter 6**. Several gaps in clinical management were voiced from the patients' view. Furthermore, despite national and various international guidelines for the management of HDP, controversy remains around the BP threshold for initiation of antihypertensive treatment and the target level for BP control in women with mild to moderate chronic or gestational hypertension during pregnancy. This was investigated in the large Control of Hypertension In Pregnancy Study (CHIPS). Although the BP threshold for initiation of antihypertensive treatment was not agreed upon, recommendations for tight BP control (dBP 85mmHg) to reduce incidence of severe hypertension during pregnancy were made. Another controversy is that of the timing of delivery for women with mild to moderate gestational hypertension or pre-eclampsia. Recommendations were made from the large 'Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation' (HYPITAT) trial for immediate delivery after 36 weeks in women with mild gestational hypertension or pre-eclampsia and a single fetus in a cephalic presentation. Since then, the national SOMANZ guidelines have incorporated this recommendation, but not all international guidelines agree on this point.

This chapter reports research into the management of the Phase 2 cohort in regard to their HDP. The aim of this study was to contextualise the women's perspectives through documentation of management and outcomes. Management was analysed according to the national SOMANZ clinical guidelines and two current controversies regarding management of HDP, namely the control of BP in mild to moderate chronic or gestational hypertension according to the CHIPS trial and timing of delivery according to the HYPITAT trial. This was the first study to analyse a prospective cohort in this way.

The prospective follow-up via medical records allowed recording of BP and management in real time. Participants' medical records were manually reviewed after each appointment, and relevant data were extracted. Maternal data included demographics, medical and obstetric history, progression of the HDP, including development of moderate to severe hypertension (systolic blood pressure (BP) ≥ 150–170 mmHg and/or diastolic BP ≥ 100–110 mmHg), severe hypertension (systolic BP ≥ 170 mmHg

and/or diastolic BP ≥ 110 mmHg) and PE. Management of the HDP, including use of antihypertensive medication, use of aspirin and time of initiation, admission to the Pregnancy Day Assessment Centre (PDAC), as well as antenatal hospital admission, were recorded. All 100 participants were followed up until delivery and neonatal data were recorded, including gestational age at delivery, birthweight and need for special or neonatal intensive care admission. There were no significant relationships between adherence and clinical outcomes reported in this study.

This manuscript is under review by **Obstetric Medicine** and is reproduced below.

Appendices relevant to this chapter are appendix 5, 6, 7, 11, 12, 13, 17 and 18.

7.2 Manuscript: Management of hypertensive disorders of pregnancy in two Australian tertiary care maternity hospitals

Under Review by **Obstetric Medicine**

Management of hypertensive disorders of pregnancy in two Australian tertiary care maternity hospitals

Amyna HELOU[1], Kay STEWART[1], Johnson GEORGE[1]

1. Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Victoria, Australia

Full title: Management of hypertensive disorders of pregnancy in two Australian tertiary care maternity hospitals.

Short title: Management of HDP in two hospitals.

Authors: Amyna HELOU[1], Kay STEWART[1], Johnson GEORGE[1]

1. Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University
381 Royal Parade Parkville, Melbourne, Australia 3052

Corresponding Author: Dr Johnson George

Email: johnson.george@monash.edu

Declarations:

Conflicting interests

The authors declare that there is no conflict of interest

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Informed consent

Potential participants were approached individually and provided with written information about the study and a questionnaire. Those who consented to the study signed a written consent form. Written informed consent was obtained from the patients for their anonymised information to be published in this article

Ethical approval

Ethical approval was obtained from participating institutions and the University. Mercy Health Human Research Ethics Committee (R12/62) 08/01/2013, The Royal Women's Hospital Research and Human Research Ethics Committee (R13/18) 12/07/2013 and Monash University Human Research Ethics Committee (CF13/117) 18/01/2013.

Guarantor

JG is the guarantor for this manuscript.

Contributorship

All authors were involved in the concept and design of the study as well as ethical approval.

AH carried out patient recruitment, data collection, writing of first draft.

AH and JG were involved with data analysis.

All authors contributed to data analysis and interpretation.

All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Acknowledgements

Our gratitude goes to the pregnant women who participated in this research. The authors would also like to thank the staff at the Mercy Hospital for Women and the Royal Women's Hospital for accommodating this research. We would also like to thank Prof Susan Walker for her guidance and comments on the manuscript, Dr Fiona Cullinane for her assistance at the Royal Women's Hospital, and Dr Ian Hunt for statistical support.

List of keywords:

pregnancy

chronic hypertension

gestational hypertension

antihypertensive agents

maternity hospitals

Management of hypertensive disorders of pregnancy in two Australian tertiary care maternity hospitals

Introduction

Hypertensive disorders of pregnancy (HDP) affect about 10% of pregnancies in Australia[1] and are a leading cause of maternal mortality and perinatal death worldwide.[2] It is estimated that 500,000 perinatal deaths and 30,000 maternal deaths are attributable to HDP annually.[3] Optimising antenatal management of HDP is core to reducing maternal and fetal risks, and a key objective of clinical practice guidelines.

The Society of Obstetric Medicine of Australian and New Zealand (SOMANZ) guidelines on management of HDP,[1, 4] form the basis for the management of HDP at the studied institutions. Both 2008 and 2014 SOMANZ guidelines recommend labetalol, methyldopa and oxprenolol as first line antihypertensive medications and hydralazine, nifedipine and prazosin as second line.[1, 4] Moreover, both guidelines advise that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are contraindicated in pregnancy.[1, 4] Unless deemed essential due to comorbidities, they also do not recommend atenolol and other highly selective beta blocker drugs as they are associated with fetal growth restriction, or thiazide diuretics, which may restrict the natural plasma volume expansion of pregnancy.[1, 4]

The Control of Hypertension In Pregnancy Study (CHIPS)[5] found no significant differences in the risk of pregnancy loss, high-level neonatal care or overall maternal complications between less-tight (target diastolic BP 100 mmHg) and tight (target diastolic BP 85 mmHg) control of hypertension. Hence the BP threshold to initiate antihypertensive treatment in pregnant women with mild to moderate hypertension remains in contention, leaving the

decision up to the treating clinician's judgement. The 2014 SOMANZ guidelines have also added a recommendation regarding the timely delivery of women with mild-moderate hypertensive disease, in light of findings from the 'Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia (PE) after 36 weeks gestation' (HYPITAT-I) trial.[6]

There is a paucity of studies investigating the prospective management of HDP in the context of clinical guidelines in Australia and internationally. The few studies that have assessed the uptake of HDP guidelines recommendations have been retrospective.[7, 8] Similarly, studies investigating the uptake of recommendations from either CHIPS or HYPITAT-I have also been scarce and have not been undertaken in an Australian context.[9, 10]

Aims

The aim of the study was to prospectively review management of HDP in an Australian cohort in the context of clinical guidelines and current evidence in the published literature regarding management controversies. The specific objectives were:

1. To evaluate compliance with clinical guidelines(4) for management of HDP during pregnancy, specifically:
    (i) appropriateness of antihypertensives used, and
    (ii) monitoring of blood pressure
2. To review the extent of use of induction of labour (IOL) at term for women with gestational hypertension (GH) or PE as per HYPITAT-I;[6] and
3. To evaluate uptake of findings from the CHIPS[5] trial regarding less-tight versus tight diastolic BP control

Methods

Study design: Prospective cohort study

Study setting: Antenatal clinics of two large tertiary maternity hospitals in Melbourne, Australia. Together, these hospitals provide antenatal care to approximately 13,000 women annually.

Inclusion criteria were:

- ≥18 years of age
- Able to understand English
- Diagnosis of a HDP (either chronic or gestational)
- Current prescription of an antihypertensive medication

Eligible participants were identified by Author 1 after reviewing the medical records of pregnant women scheduled to attend out-patient antenatal clinics (February to December 2013). Potential participants were approached individually and provided with written information about the study and a questionnaire. Those who consented to the study signed a written consent form. In-depth interviews were carried out with a subset. The medical records of all participants were prospectively reviewed until delivery.

Participants' medical records were reviewed manually by Author 1 after each appointment, and relevant data were extracted. Maternal data included demographics, medical and obstetric history, progression of the HDP, including development of moderate to severe hypertension (systolic BP (SBP) ≥ 150–169 mmHg and/or diastolic BP (DBP) ≥ 100–109 mmHg),[4] severe hypertension (systolic BP ≥ 170 mmHg and/or diastolic BP ≥ 110 mmHg)[4] and PE.[4] Management of the HDP, including use of antihypertensive medication, admission to the Pregnancy Day Assessment Centre (PDAC) as well as antenatal hospital admission were

recorded. Antihypertensive agents were classified as first-line and second-line according to the SOMANZ guidelines that were in use at the time of the study.[4]

All participants were followed up until delivery and neonatal data were also recorded, including gestational age at delivery, birthweight, and need for special or neonatal intensive care admission. Customised centiles were calculated and FGR recorded, if birthweight was less than the tenth customised centile. Centiles were calculated using the calculator devised by Mongelli *et al* specifically for the Australian population, allowing adjustment for maternal characteristics such as height and weight, ethnicity, gestational age and fetal gender.[11] One participant had a fetal death *in utero* and maternal data extraction ceased at that point. One other participant was transferred to a different maternity hospital during their pregnancy and provided additional consent to have the relevant data, including that of the baby, extracted from her medical records at the new hospital.

Target diastolic BP amongst women who had non-proteinuric chronic or gestational hypertension between 14 weeks 0 days to 33 weeks 6 days of gestation, were analysed according to the CHIPS[5] description of less-tight control (target diastolic BP, 100 mm Hg) vs tight control (target diastolic BP, 85-99 mm Hg).

Among women who reached 36 weeks gestation with mild GH or PE and a single fetus in a cephalic presentation ('HYPITAT eligible'), outcomes were compared between those managed expectantly and those managed with immediate/as soon as practicable IOL, as described in the HYPITAT-I trial.[6] Outcomes compared between groups were those reported in HYPITAT-I, namely maternal mortality, maternal morbidity (eclampsia; haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome; pulmonary oedema; thromboembolic disease; and placental abruption), progression to severe hypertension or proteinuria, and major post-partum haemorrhage (>1000 mL blood loss).[12]

Data were analysed using descriptive statistics and appropriate univariate analysis (Pearson chi-square and Student's *t*-tests) and multivariate analysis (logistic regression) using SPSS (version 26.0, IBM, New York, NY, USA). $P < 0.05$ was considered statistically significant.

Results

A total of 100 pregnant women were recruited. Among these participants, 68 had chronic hypertension (CH), while 32 had gestational hypertension (GH); these groups are compared in Table 1. Thirteen participants with CH were diagnosed during pregnancy, 10 of whom were diagnosed by their local GP at 4-9 weeks gestation. (insert Table 1)

The specific antihypertensives prescribed in this population are summarised in Table 2. Labetalol was the most common agent prescribed in CH, whereas methyldopa was the preferred agent in GH. (insert Table 2)

Table 3 describes the type of monitoring that the women in the cohort received during the pregnancy as well as the rates of PE development, episodes of severe hypertension and the need for emergency caesarean delivery. (insert Table 3)

In the only significant result found by logistic regression was that a well-timed first antenatal visit (by 12 weeks gestation) was less likely to be associated with severe hypertension –OR 0.160 (95% CI 0.037–0.683).

Of the 100 women, 68 had non-proteinuric mild-moderate gestational or chronic hypertension diastolic BP of 85-99mmHg. The remaining nine had diastolic BP reading ≥ 100mmHg at a stage prior to 33 weeks 6 days gestation. Their outcomes are compared in Table 4. (insert Table 4)

Of the 21 'HYPITAT-I eligible' women with mild GH or mild PE, 16 (76.2%) had not been delivered at 36 weeks and had no contraindication for induction of labour, such as breech or

planned caesarean. Of these, 4 (25%) appeared to have been managed with immediate/as soon as practicable IOL, while 12 (75.0%) were considered safe for expectant management and were delivered between 37 weeks (+2 days) and 39 weeks (+6 days). Of these, one woman progressed to severe hypertension and another progressed to severe PE; however, neither developed a composite severe adverse outcome, as defined by HYPITAT-I.[6] There was no significant difference in the rate of caesarean section between these groups. The FGR (< tenth centile) rate was 50% in the expectant management group and 50% in the immediate management group.

Discussion

This study showed that management of HDP was mostly consistent with current guidelines (SOMANZ[1, 4]) and evidence (CHIPS[5], HYPITAT-I[6]) at the time. This study has also highlighted that pre-pregnancy or early pregnancy consultation can ensure that women with CH are on appropriate antihypertensive medications, thus helping to reduce the potential for birth defects following inadvertent exposure in early pregnancy.[13]

In our study, more than half of the women in the CH group were using an antihypertensive medication prior to pregnancy and a little over half of these were not on a pregnancy safe medication. Nevertheless, the majority of women with CH had their antihypertensive switched to a pregnancy-safe agent by the time of their first hospital antenatal appointment, attesting to the value of pre-pregnancy consultation. Since the time this study was undertaken, there has been a stronger recommendation from several clinical guidelines to cease antihypertensives that are not classified as safe in the pre-conception period.[1, 14] The 2016 Australian guidelines for the diagnosis and management of hypertension in adults mentions pregnancy and the potential for pregnancy in women of reproductive age as a contraindication for ACEI and ARBs.[15]

The majority of women in both the CH and GH groups were prescribed a first line antihypertensive, in compliance with clinical guidelines. Methyldopa was used significantly more often in the GH group than the CH group. Although this may have been acceptable at the time,[4] current clinical recommendations are to change methyldopa to an alternative antihypertensive if treatment should continue in the immediate postpartum period, due to its potential to exacerbate post-natal depression.[14]

The timing of the first antenatal appointment was significantly later for the women in the CH group compared to the women in the GH group. This is despite that prescription of an antihypertensive would have been valid upon conception in the majority of women with CH. In our study, a later initial booking visit was more likely to be associated with an incidence of severe hypertension. A study in the UK that studied the reasons for delayed access to antenatal care, found that although there were patient-related factors such as knowledge of pregnancy, there were also administrative failures such as letters not being sent and/or received in a timely manner.[16] There is, however, a dearth of studies into why pregnant women do not access timely, free and locally available antenatal care both in the UK[17] and Australia.

The rate of admission to PDAC was as expected across both groups[18] and may have contributed to the low incidence of severe hypertensive disease in this cohort. There were, however, some women who required hospitalisation to reduce the risks of severe hypertension and/or PE for both the mother and the baby, indicating close monitoring.

The majority of women with mild to moderate non-proteinuric hypertension had their BP tightly controlled as defined by CHIPS.[5] This may have contributed to the low incidence of severe hypertension in the cohort. It also reinforces that pregnant women who require

antihypertensive treatment should be under an obstetrician model of care as recommended in the current SOMANZ guidelines.[1]

Only one-quarter of 'HYPITAT eligible' patients were delivered at 37 weeks, yet we observed a lower rate of adverse maternal outcomes in this group than what would have been anticipated by HYPITAT-I. This rate was similar to that seen in a retrospective cohort study in Australia,[7] but contrasts with results from an earlier study in the United States.[9] The SOMANZ guidelines advise considering delivery after 37 weeks but prior to 41 weeks, particularly if maternal or fetal complications have developed.[1] Many patients in this study were managed expectantly until 37 to 41 weeks, which may explain some of the observed differences in major adverse events in this cohort compared to HYPITAT-I.[6] This suggests that clinicians actively weighed up the potential maternal benefit of immediate delivery versus neonatal harm, including the long-term consequences of late preterm and early term birth. Furthermore, this indicates that the clinical practice was more aligned with the subsequent HYPITAT-II, which found that expectant management of women with mild GH or PE between 34 and 37 weeks was associated with a non-significant increase in maternal adverse outcomes, but a significant reduction in neonatal respiratory distress.[19]

It is expected that routine introduction of sFlt/PlGF ratio into clinical practice will be an important addition to the current diagnostic algorithm for PE in pregnant women with either CH or GH. The sFlt/PlGF ratio has recently been found to differentiate between the diagnosis of CH with superimposed pre-eclampsia and uncontrolled CH enabling a judgement of the need for an increase in the dose of the antihypertensive.[20] Similarly, the Preeclampsia Triage by Rapid Assay (PETRA) group recently undertook a prospective observational study of pregnant women with signs or symptoms of PE between 20 and 35 weeks gestation at 24 centres in the United States. They found that sFlt/PlGF ratio can help to predict the potential

for adverse pregnancy outcomes better than clinical markers, and thus inform timing of delivery.[21]

Strenghs and limitations

To the best of our knowledge, this is the first study to prospectively evaluate the Australian management of HDP according to the SOMANZ guidelines. Although the division between the CH and GH group was not equal, the ratio is consistent with that observed in the CHIPS trial.[5] Although recruitment was from two major tertiary maternity hospitals in Melbourne, the study was not powered to detect differences in the clinical management between groups. The low sample size also compromised the adequacy for multivariate analyses. Moreover, the women were followed up only until delivery, so if they developed postpartum PE or their hypertension persisted after 6 weeks postpartum the data were not captured. Further research involving larger numbers of participants is warranted, and would require recruitment from a larger and broader range of tertiary maternity centres.

Conclusions

In conclusion, the clinical management guidelines for HDP were followed well. Pre-pregnancy or early pregnancy counselling for women with CH helped to ensure that antihypertensive medication was switched in a timely manner to a pregnancy safe agent. Recommendations from the CHIPS trial were generally followed in this cohort. Although HYPITAT-I was available at the time of this cohort study, the clinicians were already practising according to HYPITAT-II indicating vigilance on behalf of the treating team and providing reassurance to pregnant women.

References

1. Lowe SA, Bowyer L, Lust K, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. *Aust Nz J Obstet Gyn* 2015; 55: e1-e29. DOI: 10.1111/ajo.12399.

2. World Health Organization. Maternal mortality 2016. Available from: http://www.who.int/mediacentre/factsheets/fs348/en/ accessed 11/12/2020

3. von Dadelszen P and Magee LA. Preventing deaths due to the hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2016; 36: 83-102. 2016/08/18. DOI: 10.1016/j.bpobgyn.2016.05.005.

4. Lowe SA, Brown MA, Dekker GA, et al. Guidelines for the management of hypertensive disorders of pregnancy 2008. *Aust Nz J Obstet Gyn* 2009; 49: 242-246. DOI: 10.1111/j.1479-828X.2009.01003.x.

5. Magee LA, von Dadelszen P, Rey E, et al. Less-Tight versus Tight Control of Hypertension in Pregnancy. *New Engl J Med* 2015; 372: 407-417. DOI: 10.1056/NEJMoa1404595.

6. Koopmans CM, Bijlenga D, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009; 374: 979-988. DOI: 10.1016/S0140-6736(09)60736-4.

7. Helou A, Walker S, Stewart K, et al. Management of pregnancies complicated by hypertensive disorders of pregnancy: Could we do better? *Aust Nz J Obstet Gyn* 2017; 57: 253-259. DOI: 10.1111/ajo.12499.

8. Banala C, Moreno S, Cruz Y, et al. Impact of the ACOG guideline regarding low-dose aspirin for prevention of superimposed preeclampsia in women with chronic hypertension. *Am J Obstet Gynecol* 2020; 223. DOI: ARTN 419.e1-e16 10.1016/j.ajog.2020.03.004.

9. Pauli JM, Lauring JR, Stetter CM, et al. Management of gestational hypertension - the impact of HYPITAT. *J Perinat Med* 2013; 41: 415-420. DOI: 10.1515/jpm-2012-0179.

10. de Sonnaville CMW, Hukkelhoven CW, Vlemmix F, et al. Impact of Hypertension and Preeclampsia Intervention Trial At Near Term-I (HYPITAT-I) on obstetric management and outcome in The Netherlands. *Ultrasound Obst Gyn* 2020; 55: 58-67. DOI: 10.1002/uog.20417.

11. Mongelli M, Figueras F, Francis A, et al. A customized birthweight centile calculator developed for an Australian population. *Aust N Z J Obstet Gynaecol* 2007; 47: 128-131. 2007/03/16. DOI: 10.1111/j.1479-828X.2007.00698.x.

12. Koopmans CM, Bijlenga D, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009; 374: 979-988. 2009/08/07. DOI: 10.1016/S0140-6736(09)60736-4.

13. Magee LA. Treating hypertension in women of child-bearing age and during pregnancy. *Drug Safety* 2001; 24: 457-474. DOI: Doi 10.2165/00002018-200124060-00004.

14. National Institute of Health Care and Excellence. Hypertension in pregnancy: diagnosis and management. NICE guideline 133 2019 Available from: www.nice.org.uk/guidance/ng133 accessed 30/5/2021.

15. National Heart Foundation of Australia. Guideline for the diagnosis and management of hypertension in adults – 2016. Melbourne: National Heart Foundation of Australia, 2016.

16. Haddrill R, Jones GL, Mitchell CA, et al. Understanding delayed access to antenatal care: a qualitative interview study. *Bmc Pregnancy Childb* 2014; 14. Artn 207 DOI: 10.1186/1471-2393-14-207.

17. Mitchell CA, Jones G and Anumba DOC. Why do 'high risk' women book late or not at all for antenatal care? *Brit J Gen Pract* 2015; 65: 574-574. DOI: 10.3399/bjgp15X687301.

18. McCarthy EA, Carins TA, Hannigan Y, et al. Effectiveness and safety of 1 vs 4 h blood pressure profile with clinical and laboratory assessment for the exclusion of gestational hypertension and pre-eclampsia: a retrospective study in a university affiliated maternity hospital. *Bmj Open* 2015; 5: e009492. 2015/11/20. DOI: 10.1136/bmjopen-2015-009492.

19. Broekhuijsen K, van Baaren GJ, van Pampus MG, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial. *Lancet* 2015; 385: 2492-2501. 2015/03/31. DOI: 10.1016/S0140-6736(14)61998-X.

20. Hernandez-Pacheco JA, Rosales-Zamudio CI, Borboa-Olivares H, et al. The sFlt-1/PlGF ratio as a triage tool to identify superimposed preeclampsia in women with chronic hypertension in emergency rooms. *Pregnancy Hypertension-an International Journal of Womens Cardiovascular Health* 2020; 21: 38-42. DOI: 10.1016/j.preghy.2020.04.014.

21. Barton JR, Woelkers DA, Newman RB, et al. Placental growth factor predicts time to delivery in women with signs or symptoms of early preterm preeclampsia: a prospective multicenter study. *Am J Obstet Gynecol* 2020; 222. ARTN 259. DOI: e1-e11 10.1016/j.ajog.2019.09.003.

Table 1: Baseline maternal characteristics and obstetric history (N=100)

Characteristic	CH (n=68)	GH (n=32)
Age in years, mean [±SD]	33.2 [4.8]	32.5 [5.3]
Body Mass Index n (%)		
18.5–24.9	19 (27.9)	7 (21.9)
25.0–29.9	18 (26.5)	11 (34.4)
≥30.0	31 (45.6)	14 (43.7)
Smoking status n (%)		
Current smoker	2 (2.9)	0 (0)
Ex-smoker	22 (32.4)	14 (43.7)
Never smoker	44 (64.7)	18 (56.3)
Co-morbidity n (%)		
Renal disease	7 (10.3)	0 (0)
Congenital heart disease	2 (2.9)	0 (0)
Obstetric history n (%)		
Nulliparous	32 (47.1)	14 (43.7)
Previous GH	6 (8.8)	4 (12.5)
Previous PE	15 (22.1)	4 (12.5)
Previous FGR†	10 (14.7)	1 (3.1)

† Fetal Growth Restriction < 10th centile

Table 2: Summary of antihypertensive medication (N=100)

Antihypertensive medication†	CH (n=68)	GH (n=32)
First-line n (%)		
Labetalol	40 (58.8)	5 (15.6)
Methyldopa	22 (32.4)	26 (81.3)*
Oxprenolol	2 (2.9)	0 (0)
Second-line n (%)		
Nifedipine	2 (2.9)	1 (3.1)
Prazosin	1 (1.5)	0 (0)
Secondary indication n (%)		
Phenoxybenzamine ‡	1 (1.5)	0 (0)
Atenolol§	3 (4.4)	0 (0)
Pre-conception (n=46 [67.6%) n (%)		
Methyldopa	8 (38.1)	
Labetalol	12 (57.1)	
Prazosin	1 (4.8)	
ACEI and ARBs	19 (41.3)	
Calcium channel blocker	4 (8.7)	
Beta blocker	2 (4.3)	
ADEC Category D antihypertensive pre-conception¶ n (%)	14 (20.6)	
At first antenatal visit	1 (1.5)	

† some women were initially prescribed more than one antihypertensive

‡ suspected pheochromocytoma * p=<0.001

§ two women had congenital heart disease resulting in secondary hypertension , one woman had primary chronic hypertension

¶Australian Drug Evaluation Committee Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effect.

Table 3: Antenatal monitoring and hospital admission for management of HDP (N=100)

Monitoring	CH (n=68)	GH (n=32)	p-value
Gestational week of antenatal booking appointment, mean (±SD)	13.1 (3.6)	16.0 (3.9)	<0.001
Admitted to PDAC†, n (%)	43 (63.2)	28 (87.5)	0.10
Admitted more than once	32 (47.1)	24 (75.0)	0.007
Antenatal hospital admission‡, n (%)	18 (26.5)	18 (56.5)	0.004
Management of unstable BP, n (%)	11 (16.2)	4 (12.5)	
Further evaluation of PE, n (%)	4 (5.9)	13 (40.6)	
Further evaluation of fetal growth/well being, n (%)	6 (8.8)	6 (18.8)	
Other medical/obstetric indication, n (%)	2 (2.9)	2 (6.3)	
Developed pre-eclampsia, n (%)	15 (22.1)	18 (56.5)§	<0.001
Severe pre-eclampsia, n (%)	5 (7.4)	8 (25.0)	0.386
Incidence of severe hypertension, n (%)	14 (20.6)	7 (21.9)	0.553
Emergency caesarean section, n (%)	15 (22.1)	15 (46.9)	0.012
Pre labour, n(%)	7 (10.2)	7 (21.9)	
In labour ,n (%)	8 (11.8)	8 (25.0)	
Gestational week, median (IQR)	37 (33-38)	35 (31-37)	

† Pregnancy Day Assessment Centre

‡ some women had > 1 indication for hospital admission

§ some women had an initial diagnosis for pre-eclampsia but had hypertension that was gestational in nature

Table 4: Outcomes of 'tight' vs 'less-tight' BP control (N=68)

	Tight control (N=59)	Less-Tight control (N=9)	p-value
Subtype of HDP			
CH, n (%)	49 (83.1)	8 (88.9)	0.594
GH, n (%)	10 (16.9)	1 (11.1)	
Maternal outcomes†			
Severe hypertension, n (%)	10 (16.9)	1 (11.1)	0.560
PE, n (%)	10 (16.9)	1 (11.1)	0.560
Emergency caesarean section, n (%)	10 (16.9)	2 (22.2)	0.512
Perinatal outcomes			
FGR < 10 centile, n (%)	6 (10.2)	3 (33.3)	0.115
Gestational age in weeks, mean [±SD]	38.2 [1.48]	37.2 [0.90]	0.467

† after 34 weeks gestation

CHAPTER 8

DISCUSSION OF THE MAIN RESEARCH FINDINGS AND CONCLUSIONS

8.1 Introduction

Previous chapters (**Chapters 3 to 7**) have presented in detail the work undertaken for each phase and sub-phase (retrospective cohort study, cross-sectional survey, in-depth interviews and the prospective cohort study). This chapter will discuss the main findings in relation to the thesis with some reference to the thesis objectives (**Section 1.8.1**). **Section 8.2** gives an overall discussion of the body of work included in this thesis. **Section 8.3** discusses the key findings of the thesis, including a description of their practice implications. **Section 8.4** describes what this research adds to current knowledge in the field. **Section 8.5** acknowledges the strengths and limitations of the studies included in this thesis. **Section 8.6** puts forward some recommendations in light of the findings of the studies, with future research directions outlined in **Section 8.7**. **Section 8.8** presents the conclusions of this thesis.

8.2 Overview

The work described in this thesis provides the foundation for better understanding of the management of HDP from both hospital system and patient views. It also outlines potential roles for the expansion of practice for pharmacists. The role of pharmacists in the management of HDP was largely unknown before this research was undertaken. This is despite the fact that HDP affects up to 10% of pregnancies in Australia and is a cause of major morbidity and mortality for the mother and her child, both during pregnancy and in the long term. Moreover, there was limited research around the clinical management of HDP in the hospital system, from both the hospital and patient point of view. Further to this, the rate of prescription of antihypertensive medication during pregnancy was not known from the existing literature. To address this, the management of women who were diagnosed with HDP at a tertiary maternity hospital in Melbourne in one calendar year was examined in the retrospective cohort study (**Chapter 3**). This cohort study provided a solid background of how pregnant women with HDP were managed, including the BP threshold for diagnosis, administration of low dose aspirin for the secondary prevention of pre-eclampsia, and the timing and mode of delivery; none of which had been reported in Australian obstetric literature at the time of publication of the article in **Chapter 3**. Furthermore, the cohort study provided an estimation of the number of women who are prescribed antihypertensive during pregnancy on an annual basis. Only around 20% of the women had been prescribed an antihypertensive for more than four weeks, which was deemed the minimum time to assess adherence. This then formed the basis of the sample size number for the Phase 2 project. Research into the adherence of pregnant women to antihypertensive medication and the factors related to it (or the lack thereof) was also scant. The survey, which included a nonadherence scale, was

administered to 100 pregnant women with HDP and a prescription for an antihypertensive as part of the Phase 2 prospective cohort study. The estimation of adherence to antihypertensive medication by women with any subtype of HDP had not been previously reported in the literature at the time of publication of the article in **Chapter 4**. The survey estimated a self-reported sub-optimal adherence rate of 90% but only limited information was given about the factors influencing this behaviour. Similarly, although a role for pharmacists in improving adherence did emerge, a further understanding of these factors would provide a clearer understanding of how pharmacists and other HCPs may have an impact on adherence. In-depth interviews were then utilised in a subset of women to elicit further information about the factors affecting adherence or lack thereof (**Chapter 5**). This chapter gave a deeper insight into the beliefs, attitudes and behaviours of pregnant women who are prescribed an antihypertensive medication. A breadth of views were voiced by the participating women themselves, owing to the nature of the in-depth interviews. Roles for pharmacists, obstetricians and general practitioners were identified in promoting and optimising medication adherence in the publication that forms part of **Chapter 5**. The nature of the in-depth interviews also allowed the voicing of opinions about the clinical management of the women from their perspective (**Chapter 6**). A varied scope of views came from pregnant women of different ages, parities, stages of pregnancy, as well as HDP subtypes and severity. Several gaps were identified in the management of HDP from the perspective of the women themselves. The women wanted to be included in management decisions when appropriate. The publication that forms part of **Chapter 6** also suggested roles for pharmacists, obstetricians, midwives and general practitioners in optimising patient management. In particular, this chapter identified that pharmacists could assist with the long-term BP follow-up of women after a pregnancy complicated by gestational hypertension or pre-eclampsia, due to ongoing increased cardiovascular risks. The same women were followed-up in a prospective cohort model (**Chapter 7**). This was important to contextualise the women's perspectives reported in **Chapters 4-6** through documentation of management and outcomes. This chapter also identified a role for the pharmacists in pre-pregnancy counselling for women with chronic hypertension, including triggering a switch to a safer antihypertensive agent during pregnancy.

Findings from the research presented in this thesis have been published in obstetric, obstetric medicine and general medicine journals. The Australian Journal of Pharmacy has also reported on the findings from the article in **Chapter 4.**

In this chapter, the overall findings from the thesis are discussed including their significance in the field of knowledge and the potential of this research to inform strategies for the optimisation of management and medication use in women with HDP through a multidisciplinary team including pharmacists to improve the outcomes of the mother and her child both during the pregnancy and in the long-term.

8.3 Discussion of main research findings

The retrospective cohort study (**Chapter 3**) provided an insight into the clinical management of HDP. It also fulfilled the objective of providing an understanding of the management of hypertensive disorders of pregnancy in the Australian context. This involved investigating clinician compliance to Australian guidelines, specifically: BP thresholds for initiation of antihypertensive therapy; appropriateness of medication regimens; and use of aspirin in women with known risk factors for development of pre-eclampsia.

Overall, the Australian SOMANZ guidelines were followed well in terms of appropriateness of antihypertensive medication regimens and thresholds for the initiation of antihypertensive therapy. There was, however, room for improvement in timely prescription of low-dose aspirin before 16 weeks of gestation for the prevention of pre-eclampsia. Delayed booking for the first antenatal appointment of women with known risk factors for the development of pre-eclampsia was found to contribute to this. Ideally, pregnant women with known risk factors for the development of pre-eclampsia, including those with chronic hypertension, should be seen by a doctor before 12 weeks gestation. More recent clinical advice (Chappell et al) is that a sensible approach would be to start aspirin before 16 weeks' gestation, but to still offer it up until 22 weeks (101). This, however, was not the recommendation at the time of the study or its publication.

Triaging of women with known risk factors, namely experience of pre-eclampsia in a previous pregnancy or chronic hypertension, to the midwifery care model might also have contributed to the oversight of a timely aspirin prescription. The triaging was done by a team of midwives including the head midwife and took into consideration the level of risk of pre-existing conditions on the pregnancy. The system is based on a three-level risk scale, low, medium and high. Unfortunately, for some of the women in the study, chronic hypertension was not noticed as carrying high risk when they were triaged to midwifery care and thus missed out on the appropriate management early on in the pregnancy. This does not only pertain to the timely prescription of aspirin, but also the close monitoring of the fetus and for signs of pre-eclampsia. Similarly, being managed through the midwifery model gave the women a false sense of safety and were surprised when they heard that they were developing pre-eclampsia or that their hypertension was difficult to control.

An additional finding related to the management of HDP was the timing of delivery of pregnant women with mild gestational hypertension or mild pre-eclampsia. Although the HYPITAT recommendation was not yet a recommendation in the SOMANZ guidelines at the time of this study, it is important to note that the obstetricians at the studied centre were aware of the HYPITAT trial findings and considered them when deciding to induce labour at 37 weeks or continue with expectant management. They weighed up the risks versus benefits for both mother and baby, and this resulted in minimal severe adverse outcomes.

The survey of pregnant women with HDP (**Chapter 4**), which incorporated a nonadherence scale, allowed the estimation of nonadherence to antihypertensive medication during pregnancy and factors contributing to it. This fulfilled the second thesis objective, which was to estimate the rate of nonadherence to antihypertensive therapy during pregnancy. Rates of nonadherence were found to be higher than those reported in the adult hypertensive population. Moreover, the rate was higher than that reported in other chronic conditions during pregnancy. There were no published works on medication adherence in any gestational condition at the time of this study. The rates of nonadherence were found to be similar between women with pre-existing chronic hypertension and gestational hypertension. Concerns and reasons for nonadherence to antihypertensives during pregnancy were also similar across women with any subtype of HDP. It was found that the nonadherence rates were not affected by the common reasons for nonadherence in the general population, such as complexity of medication regimen, and instead was influenced by perceptions of risks.

The in-depth interviews (**Chapters 5 and 6**) provided a greater insight into the women's perspectives on both adherence to medication and the management of their HDP. This achieved the third objective to understand the women's perspectives on adherence to medication and management of their hypertensive disorder of pregnancy.

The interviews provided a rich understanding of the attitudes, behaviours and adherence of pregnant women diagnosed with HDP and prescribed an antihypertensive, from the women themselves during their pregnancy. Understanding of HDP and their implications, risks versus benefits of antihypertensive medication during pregnancy, and trust in medical professionals were all found to influence adherence in this population. These findings were complementary to what was found in **Chapter 4**. Furthermore, attitudes towards monitoring of HDP identified gaps in the management of the women from their point of view. This included trust in the hospital system and attitudes towards self-monitoring of blood pressure, pregnancy day centre and hospital admissions. Attitudes and perceptions towards development and management of complications including pre-eclampsia and fetal growth restriction and varied perceptions of pregnant women with chronic hypertension also revealed gaps in management from the women's perspective.

The prospective cohort study (**Chapter 7**) documented the management and outcomes of the women and thus contextualised the perspectives of the women with regard to the management of their HDP, fulfilling the fourth thesis objective. Admissions to the pregnancy day centre were appropriate, suggesting that women at risk of pre-eclampsia or worsening hypertension were closely monitored. Appropriate rates of antenatal admissions to hospital for the management of severe HDP confirmed this finding. The triangulation of the survey, in-depth interviews and the prospective cohort study provided a deep understanding of medication use for HDP during pregnancy from the view of both patients and the health system. Documentation of management and outcomes also allowed the

identification of further gaps that have the potential for improvement. Although clinical guidelines were generally well followed, this study highlighted the potential for improvement in the management of women with chronic hypertension, which corroborated the perceptions of the women as reported in the in-depth interviews. Data from the cohort were analysed in light of two current controversies: namely, the target diastolic BP in pregnant women with mild to moderate chronic or gestational hypertension treated with antihypertensives (CHIPS); and the timing of delivery for women who have reached 36 weeks gestation and have mild to moderate gestational hypertension or pre-eclampsia (HYPITAT).

8.4 The significance of this research

Only a limited and incomplete body of evidence on medication use and adherence of pregnant women with HDP from their perspective was available when this PhD commenced. Moreover, research regarding in-practice clinical management, from both the health system and patient perspectives, was also limited. The findings of this PhD thesis add to current knowledge and evidence within published literature surrounding medication use and management for HDP. The retrospective cohort study confirmed that local clinical management guidelines were largely being followed; however, there was an oversight in the timely prescription of low-dose aspirin for pregnant women who were at high risk of developing pre-eclampsia, including women with chronic hypertension. The rate of uptake of prescription of low-dose aspirin for these women was 12%. This had previously only been estimated by expert opinion (247). Similarly, this low uptake of prescription has more recently contributed to research into alternative approaches to pre-eclampsia screening and prevention, including the use of biomarkers in treatment algorithms (248). The finding that the clinicians were delaying the timing of delivery in pregnant women with mild gestational hypertension or pre-eclampsia as per the HYPITAT trial (158) was an early indication from the field that clinicians appropriately consider the likely maternal risk compared to infant risk in each individual case. Subsequently, this was a recommendation of HYPITAT-II (249) that had not been previously reported at the time of publication of this research.

The survey estimated nonadherence to antihypertensive medication during pregnancy. The findings suggested that self-reported adherence to medication during pregnancy is low (32, 33). Moreover, pharmacists are only involved with the dispensing of antihypertensive medication with limited interaction with pregnant women either pre-conception or during pregnancy. This study identified a role for pharmacists in the optimisation of medication adherence during pregnancy.

The in-depth interviews gave a deep and an innovative perspective on medication use, adherence and clinical management of HDP from the patient's view. Factors associated with the attitudes, behaviours and adherence of pregnant women diagnosed with HDP and being treated with antihypertensive medication and agents to prevent pre-eclampsia, including low-dose aspirin, were further examined.

The role of pharmacists in promoting and optimising medication adherence was reiterated in this phase of the study. This was also found to be incumbent on general practitioners, obstetricians and obstetric physicians during pregnancy. The women's views on clinical management gave a unique insight into how they interpreted medical management of a high-risk pregnancy. The demonstration of gaps in clinical management from their perspective informed the need to consider the patient view in the management of HDP. These findings supported evidence found in the literature which investigated other facets of HDP management (250, 251). The study identified a need for pharmacists to play an active role in the education of women who have chronic hypertension and are of reproductive age. Timely review and modification of antihypertensive medication, if appropriate to a safer alternative, when planning pregnancy is imperative. Pharmacists can also assist with BP monitoring during pregnancy for women with any subtype of HDP. The study also recognised the ongoing role that the pharmacist can play in monitoring BP postpartum for women who have had gestational hypertension or pre-eclampsia during pregnancy. This assists education of the patient about their future cardiovascular risk and the timely diagnosis of potential chronic hypertension, supporting evidence from recent studies (182, 252) and a recent scientific statement from the American Heart Association (253).

The prospective study contextualised the patients' views and clinical outcomes and reaffirmed the need to focus on the timely switch of antihypertensive to a safer alternative in women with chronic hypertension. The clinical guidelines (6) mention the need for an obstetric care model to manage women with chronic hypertension, regardless of the need for antihypertensive treatment. The guidelines acknowledge the importance of a team approach, especially the role of midwives, along with obstetricians and obstetric physicians to provide the best chance of optimal outcomes for mother and baby (6). It is therefore important that women with HDP be managed by the appropriate model of care.

8.5 Strengths and limitations

The strengths of this PhD project include the provision of an overall understanding of the management and medication use during HDP from the perspective of a pharmacist. This work is the first to investigate the in-practice clinical management of HDP in an Australian context. It is also the first to quantify the uptake of timely prescription of low-dose aspirin for the prevention of pre-eclampsia in women at risk of developing the condition, a rate that was previously estimated by experts in the field. Approximately 20% of pregnant women with HDP get treated with anti-hypertensive medication during pregnancy, a rate that was not previously reported and assisted in gaining an understanding of medication use by women with HDP, especially from a pharmacist's perspective. Furthermore, adherence and barriers to medication adherence during HDP were studied using both quantitative and qualitative means. To the best of my knowledge, this had not been previously studied in-depth. Knowing that a sound understanding of the condition, a positive

risk/benefit balance regarding antihypertensive medication use during pregnancy, and trust in the health care professional contribute to adherence not only has the potential to inform future interventional studies, but also improve pharmacy practice. Additionally, the knowledge of HDP treatment and management is not well known amongst pharmacists. The research reported in this thesis has the capacity to bridge the gap as it indicates practical ways in which pharmacists may be part of the optimisation of HDP management, especially during the pre-conception and the long-term postpartum periods.

The research was limited by funding and time. Only two tertiary maternity sites were studied, both of which were in Victoria, therefore the extrapolation to other settings should be with caution. Given the geographical distance to a third site, especially in the absence of sufficient staffing for recruitment, adding another site for the prospective study was prohibitive. Hence the prospective study was not able to be powered to detect differences in clinical obstetric and neonatal outcomes. Similarly, a larger sample size may have assisted in detecting statistically significant differences between adherent and non-adherent groups, assuming that more women would self-report optimal adherence. Unlike some countries, Australia does not have a prescription record database across primary and secondary/tertiary care settings that is easily available. Although the literature review (**Chapter 2**) was not written as a systematic review, it did examine a broad array of topics related to the management of hypertensive disorders of pregnancy and medication use in pregnancy to provide a narrative overview of the field of research that was undertaken as part of this thesis. Such a systematic review was beyond the scope of this thesis. However, a systematic review of these two broad topics seperately would be important for future research. Survey administration was done in person and on paper as online surveys were not commonplace at the time of recruitment. Although the Phase 2 participants were from various cultural backgrounds, the exclusion of non-English speaking women, including newly arrived Australians and women from refugee backgrounds made it difficult to extrapolate the results to the whole of the maternal population in Melbourne. Lastly, all the studies were observational in nature and were not controlled for many potential confounding factors. Designing and implementing interventions targeting the issues identified in the retrospective and prospective studies were beyond the scope of the PhD project.

8.6 Recommendations

The results of this thesis highlight some points that should be considered when designing an intervention model for optimising HDP management - pre-conception, during pregnancy and in the long-term postpartum. There are implications for various healthcare professionals including community pharmacists, obstetricians, obstetric physicians, midwives, GPs and cardiologists. Primarily, better collaboration and involvement of these healthcare professionals needs to be established for managing HDP during pregnancy and beyond. The women themselves should also be given an opportunity to contribute to decision making in various aspects of HDP management

including appropriateness of antihypertensive treatment, close monitoring of HDP, timing and mode of delivery, as well as long term follow-up.

This research has revealed two main stages of HDP management where both the community pharmacist and the GP can play a role in optimising management. The first is pre-conception in a woman of reproductive age who has chronic hypertension. This is especially important as the timing of the initial antenatal appointment can be after 16 weeks gestation in many cases. The GP and pharmacist can educate these women about:

- the potential risks of pregnancy so that they can be aware and vigilant,
- the importance of close monitoring and optimal BP control during pregnancy,
- the signs of pre-eclampsia, and
- the importance of adherence to antihypertensives if prescribed.

The GP can initiate low dose aspirin in a pregnant women with chronic hypertension before 16 weeks for the prevention of pre-eclampsia. Pharmacists should be aware of this indication and be equipped to counsel women about this role of aspirin during pregnancy. The pharmacist is also in a position to initiate the switch of an antiypertensive to a safer alternative, pre-conception, in collaboration with the woman's GP.

The second stage is in the long-term postpartum period. Education about the future cardiovascular risk in pregnant women who had gestational hypertension or pre-eclampsia should be offered, firstly by the obstetrician and then followed up by GPs and pharmacists. Both of these community-based HCPs can integrate the long term follow-up of BP for these women in their existing practice. Unfortunately, this does not currently take place. There needs to be a system where these women are identified. This can initially be done via the discharge summary that the GP receives postpartum. The patient is then categorised as having had gestational hypertension or pre-eclampsia, BP should be checked at each routine GP visit, and by referral to community pharmacist if more frequent BP checks are required. (This is discussed further in **section 8.7**.) Any future referral to a cardiologist should acknowledge the history of gestational hypertension or pre-eclampsia, a point raised by cardiologists at the Victorian Heart Institute (254).

Role expansion and upskilling for community pharmacists via continuing professional development by HCPs (including pharmacists) who have knowledge of the management of HDP and current resources is required. Knowledge and use of resources, including the SOMANZ guidelines (6) and the Australian Medicines Handbook (142), would assist pharmacists to counsel on antihypertensive use during pregnancy, use of aspirin during pregnancy and BP monitoring both during pregnancy and in the long term. Including a short module about pharmacists' roles in HDP management (that have been

outlined in this thesis) either in the undergraduate Bachelor of Pharmacy course or the intern program would also equip new pharmacy graduates with the appropriate knowledge.

The obstetricians, obstetric physicians and midwives should inform any women with HDP of the importance of close monitoring, optimal BP control during pregnancy, signs of pre-eclampsia, timing and mode of delivery and other facets of HDP management. This information should be communicated clearly to women with any subtype or severity of HDP, with an opportunity to ask questions and be part of the decision- making. The importance of adherence to antihypertensives, if prescribed, should also be emphasised. Inclusion of the hospital pharmacist with regard to optimisation of adherence, even in an outpatient setting, is also recommended.

Self-monitoring of BP should be encouraged by all healthcare professionals, including pharmacists, during pregnancy and beyond to encourage BP control postpartum in women with chronic hypertension and prevent severe cardiovascular events. This may also be used as a means for BP follow-up for women who had gestational hypertension or pre-eclampsia.

8.7 Future research directions

This thesis identified several areas of potential future research to better understand the best ways to optimise HDP management and medication use. Firstly, larger longitudinal cohort studies to detect statistical differences between clinical management and maternal and neonatal outcomes to enable the design of interventional models to optimise management are required. Further research into the causes of pre-eclampsia to assist in early diagnosis and timely management of women developing the condition, with a focus on including the patient in the conversation. Continuing research into biomarkers for the early detection of pre-eclampsia will not only assist in the early management of pre-eclampsia, but will also remove a lot of the anxiety associated with developing this condition. Additional qualitative research, including follow-ups at various stages of pregnancy to explore patients' perspectives and behaviours regarding self-monitoring of blood pressure, biomarker screening for pre-eclampsia, use of antihypertensive medication during breastfeeding and follow up for future cardiovascular risk are also required. Intervention studies, including RCTs of tools (e.g. consumer medicines information) and models of care incorporating patient perspectives, working towards having patient involvement in decision-making. This can involve work with the TGA to change the wording of the pregnancy labelling and Consumer Medicines Information leaflets, rendering the information more useful for the women.

Research into the readiness of pharmacists for education and integration into the care of women with HDP or a history of HDP is also required. Further to the recommendations for role expansion of pharmacists in section 8.6, research into an integrated model involving the GP, pharmacist and patient is required for the optimal reduction of cardiovascular risks in the long term postpartum. There are many facets of research required for this model. Firstly, research into the accuracy and quality of the

information that is received by the GP in the discharge summary with regard to gestational hypertension or pre-eclampsia is required. Collaboration between the GP and the community pharmacist should also be explored. Involving the patient in the follow-up, giving options of self-monitoring of BP and educating about the potential cardiovascular risks would also inform this model. Research into the possibility of making this a patient-centred model may also make this more feasible for the women to follow.

8.8 Conclusions

This thesis has identified evidence of gaps in the management of pregnant women with HDP. An increased focus by GPs and community pharmacists on women of reproductive age who have chronic hypertension is required. The women need to be made aware of potential risks during pregnancy to allow them to make informed decisions about their management and medication adherence, if they are prescribed antihypertensive treatment. Timely switching of the antihypertensive to an agent that is safer in pregnancy, timely booking of first antenatal hospital appointment, timely prescription of aspirin for the prevention of pre-eclampsia, and close monitoring of BP and signs of pre-eclampsia throughout the pregnancy through an interdisciplinary obstetric model of care is warranted. Moreover, women with gestational hypertension or pre-eclampsia during pregnancy should be informed of the potential for future cardiovascular risks. Plans for BP follow up postpartum should be made in collaboration with the women's GP and community pharmacist. Finally, empowerment of all women with HDP to take an active role in their cardiovascular health may potentially improve outcomes in subsequent pregnancies and general health outcomes postpartum.

Appendices

Appendices for Chapters 3-7

Appendix 1 – Monash University Human Research Ethics Committee approval letter

(Phase 1 – Chapter 3)

Appendix 2 – Mercy Health Human Research Ethics Committee approval letter

(Phase 1 – Chapter 3)

Appendix 3 – ICD-10 codes (Phase 1 – Chapter 3)

Appendix 4 – Data collection form (Phase 1 – Chapter 3)

Appendix 5 - Monash University Human Research Ethics Committee approval letter

(Phase 2 – Chapter 4-7)

Appendix 6 - Mercy Health Human Research Ethics Committee approval letter (Phase 2 – Chapters 4-7)

Appendix 7 - Patient Information and Consent Form whole project Mercy Hospital for Women (Phase 2 – Chapters 4-7)

Appendix 8 - Patient Information and Consent Form interviews only Mercy Hospital for Women (Phase 2 – Chapters 4-6)

Appendix 9 – Survey Mercy Hospital for Women (Phase 2 – Chapter 4)

Appendix 10 – Interview topic guide Mercy Hospital for Women (Phase 2 – Chapters 5 & 6)

Appendix 11 - Data collection form Mercy Hospital for Women (Phase 2 – Chapter 7)

Appendix 12 - The Royal Women's Hospital Human Research Ethics Committee approval letter (Phase 2 – Chapters 4-7)

Appendix 13 - Patient Information and Consent Form whole project Royal Women's Hospital (Phase 2 – Chapters 4-7)

Appendix 14 - Patient Information and Consent Form interviews only Royal Women's Hospital (Phase 2 – Chapters 4-6)

Appendix 15 – Survey Royal Women's Hospital (Phase 2 – Chapter 4)

Appendix 16 – Interview topic guide Royal Women's Hospital (Phase 2 – Chapters 5 & 6)

Appendix 17 - Data collection form Royal Women's Hospital (Phase 2 – Chapter 7)

Appendix 18 – Consent to release medical information Barwon Health (Phase 2 – Chapter 7)

Appendix 1 – Monash University Human Research Ethics Committee approval letter (Phase 1 – Chapter 3)

MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

Human Ethics Certificate of Approval

Date:	**11 January 2011**
Project Number:	**2010001885**
Project Title:	**Retrospective cohort study on management of pregnant women with hypertension: maternal and neonatal outcomes**
Chief Investigator:	**Dr Johnson George**
Approved:	**From: 11 January 2011 To: 11 January 2016**

Terms of approval

1. The Chief investigator is responsible for ensuring that permission letters are obtained, if relevant, and a copy forwarded to MUHREC before any data collection can occur at the specified organisation. **Failure to provide permission letters to MUHREC before data collection commences is in breach of the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research.**
2. Approval is only valid whilst you hold a position at Monash University.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. **Complaints:** The researchers are required to inform MUHREC promptly of any complaints made about the project, whether the complaint was made directly to a member of the research team or to the primary HREC.
6. **Amendments to the approved project (including changes in personnel):** Requires the submission of a Request for Amendment form to MUHREC and must not begin without written approval from MUHREC. Substantial variations may require a new application.
7. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
8. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. This is determined by the date of your letter of approval.
9. **Final report:** A Final Report should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected date of completion.
10. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by MUHREC at any time.
11. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

Professor Ben Canny
Chair, MUHREC

cc: Mrs Amyna Helou

Postal – Monash University, Vic 3800, Australia
Building 3E, Room 111, Clayton Campus, Wellington Road, Clayton
Telephone +61 3 9905 5490 Facsimile +61 3 9905 3831
Email muhrec@adm.monash.edu.au www.monash.edu/research/ethics/human/index/html
ABN 12 377 614 012 CRICOS Provider #00008C

Appendix 2 – Mercy Health Human Research Ethics Committee approval letter (Phase 1 – Chapter 3)

Mercy Health
Care first

December 20 2010

Dr Johnson George
c/o Mrs. Amyna Helou
9B King Street
Bulleen
VIC 3105

Dear Mrs Helou,

R10/48: Retrospective cohort study on management of pregnant women with hypertension maternal and neonatal outcomes.

I am pleased to advise that your application has been considered by members of the Human Research Ethics Committee Expedited Review Working Party and has been granted approval.

This approval is effective immediately and enables you to commence the study, but is subject to the ratification by the Mercy Health HREC and Mercy Health Board.

In particular, the following documentation is approved for use:

Research Methodology	Dated November 29 2010
Data collection form	Dated November 2010

The full Human Research Ethics Committee will be advised of the study at its next meeting to be held in February 8 2011. You will receive a formal letter of approval from the Board following its March 1 2011 meeting.

In accordance with the NHMRC National Statement on Ethical Conduct in Human Research (2007), approval is subject to:

- Immediate notification of any unforeseen events that may affect the continuing ethical acceptability of the project;
- Notification and reasons for ceasing the project prior to its expected date of completion;
- The completion of a progress report at 6 months and then annually for the duration of the project; (progress report attached);
- Human Research Ethics Committee approval of any proposed modifications to the project;
- The submission of a final report and papers published on completion of the project.

Mercy Health
678 Victoria Street, Richmond Victoria 3121 Phone: (03) 8416 7777 Fax: (03) 8416 7888 mercy.com.au ABN 77 191 901 062

Please also note:

- The Principal Investigator upon leaving the Institution must inform the Human Research Ethics Committee as to the nominated person to replace him/her.

If you have any queries, please do not hesitate to contact me on 8458 4808.

Yours sincerely,

Carole Branch
Administrative Officer, Mercy Health Human Research Ethics Committee.

Appendix 3 – ICD-10 codes (Phase 1 – Chapter 3)

APPENDIX III

ICD-10 codes used for recruitment for Phase 1

Diagnosis	ICD-10 codes
Pre-existing hypertension	010.0
Unspecified pre-existing hypertension	010.9
Pre-existing hypertension with superimposed preeclampsia	011
Gestational hypertension without significant proteinuria	013
Gestational hypertension with significant proteinuria	014
Moderate preeclampsia	014.0
Severe preeclampsia	014.1
Unspecified preeclampsia	014.9
Eclampsia	015
Unspecified maternal hypertension	016

Appendix 4 – Data collection form (Phase 1 – Chapter 3)

DATA COLLECTION FORM

Patient ID _____

SECTION A: Maternal Data

Maternal Demographics

Age	
Weight	
BMI	
Smoking status	

Maternal Medical History

Pre-existing medical conditions (including hypertension; time of diagnosis; duration of therapy)	
Current medications - Change of antihypertensive prior to/during pregnancy - Aspirin/calcium	
Family history of pregnancy induced hypertension (first degree relatives)	

Details of current pregnancy

Parity and Gravidity	
Single ☐	Multiple pregnancy ☐
History of hypertension in previous pregnancy	
Presence of other pregnancy complications (uteroplacental vasculopathy, placental abruption, IUGR, fetal distress)	

Vaginal birth ☐ Spontaneous onset of labour? Induction of labour? Indication:	Caesarean birth ☐ Indication:
Date of delivery	

Details of previous pregnancy (ies)

History of hypertension in previous pregnancy	Yes ☐	No ☐
Presence of other pregnancy complications (uteroplacental vasculopathy, placental abruption, IUGR, fetal distress)		
Past number of caesarean deliveries		
Past number of normal deliveries		

SECTION B: Neonatal Data

Livebirth	Yes ☐	No ☐
Gestational age at delivery		
Birthweight		
Apgar score		
Presence of any other complications	Yes ☐ If Yes:	No ☐
NICU/SCN admission	Yes ☐ If Yes:	No ☐

SECTION C: HYPERTENSION

BP recordings and correlation with medication prescribed

Date	Gestational week	BP reading (mmHg)	Measurement method	Medication and dose prescribed	Reason for changing medication

Diagnosis of hypertension

Reading at which hypertension was diagnosed	
Gestational week of diagnosis	
Initial subtype of HDP	
Subsequent subtype of HDP	
Measures used to diagnose pre-eclampsia (proteinuria, uric acid, LFTs)	

Management of hypertension

Reading at which anti-hypertensive medication was initiated		
Target BP		
Initial medication prescribed		
Initial prescriber	Obstetrician ☐ Physician ☐	Registrar ☐ GP ☐
Initial model of care		
Other prescribers involved in the management of high BP	Obstetrician ☐ Physician ☐	Registrar ☐ GP ☐

Other relevant lab data during the pregnancy (e.g. proteinuria, LFTs, platelets)

Appendix 5 – Monash University Human Research Ethics Committee approval letter (Phase 2 – Chapters 4-7)

MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

Human Ethics Certificate of Approval

Date:	**15 January 2013**
Project Number:	**CF13/117 - 2013000039**
Project Title:	**Treatment of high blood pressure during pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women**
Chief Investigator:	**Dr Johnson George**
Approved:	**From: 15 January 2013 To: 15 January 2018**

Terms of approval

1. The Chief investigator is responsible for ensuring that permission letters are obtained, if relevant, and a copy forwarded to MUHREC before any data collection can occur at the specified organisation. **Failure to provide permission letters to MUHREC before data collection commences is in breach of the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research**.
2. Approval is only valid whilst you hold a position at Monash University.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. **Complaints:** The researchers are required to inform MUHREC promptly of any complaints made about the project, whether the complaint was made directly to a member of the research team or to the primary HREC.
6. **Amendments to the approved project (including changes in personnel):** Requires the submission of a Request for Amendment form to MUHREC and must not begin without written approval from MUHREC. Substantial variations may require a new application.
7. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
8. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. This is determined by the date of your letter of approval.
9. **Final report:** A Final Report should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected date of completion.
10. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by MUHREC at any time.
11. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

Professor Ben Canny
Chair, MUHREC

cc: Mrs Amyna Helou, Assoc Prof Kay Stewart, Prof Susan Walker, Assoc Prof Kath Ryan

Postal – Monash University, Vic 3800, Australia
Building 3E, Room 111, Clayton Campus, Wellington Road, Clayton
Telephone +61 3 9905 5490 Facsimile +61 3 9905 3831
Email muhrec@monash.edu http://www.monash.edu.au/researchoffice/human/
ABN 12 377 614 012 CRICOS Provider #00008C

Appendix 6 – Mercy Health Human Research Ethics Committee approval letter (Phase 2 – Chapters 4-7)

Mercy Health
Care first

8 January 2013

Dr Johnson George
Lecturer
Centre for Medicine Use and Safety
Department of Pharmacy Practice
Monash University
381 Royal Parade
Parkville
VIC 3052

Dear Dr George

Re: R12/62: Treatment of High Blood Pressure During Pregnancy. Beliefs, experiences, attitudes and behaviours of pregnant women

I am pleased to advise that your amendments comply with the requirements of the Human Research Ethics Committee meeting of 11 December 2012 and as such you may now commence with the study. Specifically, the following documentation is approved:

Module One	Version 3 Dated January 2013
Appendix 1 Participant Explanatory Statement & Consent Form	Version 3 Dated 4 January 2013
Appendix 2 Participant Explanatory Statement & Consent Form (for In-depth Interviews)	Version 3 Dated 4 January 2013
Appendix 4 Questionnaire	Dated December 2012
Appendix 5 Interview Topic Guide	Dated December 2012
Appendix 6 Data Collection Form	Dated December 2012

The Human Research Ethics Committee is constituted and functions in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007).

Approval by the Mercy Health Human Research Ethics Committee is valid for up to 3 years from the date of this letter. That is, the project should be completed by the approval expiry date, which is **8 January 2016**. Should it become apparent that an extension of the 3-year period is required, the principal researcher should apply, in writing, through the Administrative Officer of the Human Research Ethics Committee. Please note that the research project should be commenced within 12 months from the date of this letter.

Would you kindly advise me the date that you commence your research.

Mercy Health
Level 2, 12 Shelley Street, Richmond Victoria 3121 Phone: +61 3 8416 7777 Fax: +61 3 8416 7888 mercyhealth.com.au ABN 77 191 901 062

In accordance with the NHMRC Guidelines, approval is subject to:

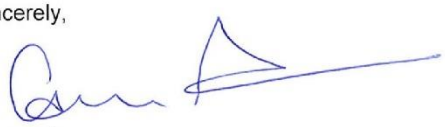
1. Immediate notification to the Administrative Officer, The Mercy Health Human Research Ethics Committee and sponsor, of any serious adverse effects on participants;
2. Immediate notification of any unforeseen events that may affect the continuing ethical acceptability of the project;
3. Notification and reasons for ceasing the project prior to its expected date of completion;
4. The completion of a progress report at 6 months and then annually for the duration of the project; (progress report attached);
5. The Mercy Health Human Research Ethics Committee approval of any proposed modifications to the project;
6. The submission of a final report and papers published on completion of the project.

Please also note:

7. Consent Forms must be available for audit by the Mercy Health Human Research Ethics Committee and retained for the period required by law;
8. The Principal Investigator upon leaving the Institution must inform the Mercy Health Human Research Ethics Committee as to the nominated person to replace him/her.

If you have any queries, please do not hesitate to contact me on 8458 4808.

Yours sincerely,



Carole Branch
Administrative Officer
Mercy Health Human Research Ethics Committee

Cc:Ms Amyna Helou, 9B King St, Bulleen, VIC 3105

Appendix 7 – Patient Information and Consent Form Phase 2 whole project Mercy Hospital for Women (Chapters 4-7)

Appendix 1: PICF for 'Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women'

MONASH University

Mercy Health
Care first

Participant explanatory statement and consent form

Full Project Title: Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women

Version 3 Dated January 4 2013

Site: Mercy Hospital for Women

Principal Researcher: Dr Johnson George

Associate Researchers: A/Prof Kay Stewart, Prof Susan Walker, A/Prof Kath Ryan, Amyna Helou

This 'Participant explanatory statement and consent form' contains NINE (9) pages. Please ensure you have all the pages

Part 1 What does my participation involve?

1. Introduction

You are invited to participate in this study because you have been prescribed an anti-hypertensive medication and indicated in the hospital privacy consent form that you are willing to be contacted for research purposes. It is hoped that your involvement will help improve the management of hypertension during pregnancy. Your contribution will also aid future research.

Please read this information leaflet carefully. Please do not hesitate to ask any questions about the information in this document. You may also want to discuss the information with a relative, friend or local health worker. Please feel free to do this.

Once you have understood the project information and if you agree to take part in the project, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you have read and understand the information and that you agree to participate in the research project

You will be given a copy of the 'Participant explanatory statement and consent form' to keep for your records.

2. What is the purpose of this research?

Hypertension is a condition that affects around 10% of pregnancies in Australia. Unfortunately, there is no information on the management of hypertension in pregnancy from the patient's perspective and how this influences behaviours and attitudes towards medication. It is hoped that by sharing your experiences, you will help to provide other women with support and informative data. The results of this research will also be used to assist Amyna Helou to obtain her PhD titled 'Adherence of pregnant women to anti-hypertensive medication'.

3. What does participation in this research involve?

Your participation in this study will only begin once you have read this Participant Information leaflet and signed the consent form. Participation in this study involves you completing a questionnaire. The questionnaire will seek information about yourself, your hypertension and your medication. It may take approximately 10 minutes for you to complete the questionnaire. You can complete the questionnaire when you are in the waiting area of the out-patient department or at home. Please leave the completed survey in the box provided or return it in the reply-paid envelope supplied. Information relating to your progress during the rest of the pregnancy and neonatal outcomes will also be collected for the purpose of this study.

You may decide not to answer some or all of the questions.

After completing the questionnaire, you may be invited to participate in a one-to-one interview around the same topic as this survey.

The decision to take part in this more in-depth interview is entirely up to you. You will be asked to sign another consent form for this part of the research if you do decide to take part in the one-to-one interview

You will not be paid for your participation in this research.

4. Other relevant information about the research project

The overall number of women participating in this study is 100 across two hospitals, Mercy Hospital for Women and Royal Women's Hospital. Approximately half of the participants will be from the Mercy Hospital for Women. This project involves researchers from Monash University, the Mercy Hospital for Women and the Mother and Child Health Research Centre, La Trobe University.

5. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Before you make your decision, a member of the research team will be available to answer any questions you have about the research project. You can ask for any information you want. Sign the

Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether or not to take part, or to take part and then withdraw, will not affect your routine care for the remainder of your pregnancy nor for any future pregnancy, your relationship with professional staff or your relationship with the Mercy Hospital for Women.

6 What are the possible benefits of taking part?

We cannot guarantee or promise that the information obtained in this study will directly benefit you but it is hoped to help women like you in the near future regarding the use of blood pressure medications during pregnancy. It is also hoped that the data collected from this study will help inform health professionals of your concerns and optimise management of hypertension during pregnancy. If during this research it becomes evident that there is a concern with your blood pressure management, we will, with your permission, contact the treating team/doctor to advise them of this.

7 What are the possible risks and disadvantages of taking part?

There are no foreseeable risks associated with participation in this study. The survey is straightforward and we will not be asking any sensitive or intrusive questions. Your identity will remain anonymous in any publication resulting from the study.

At no stage of the survey are you obliged to answer any question and you may withdraw from completing the survey at any time. There is no right or wrong answer. There will be no consequences for not answering any given question.

8 What if I withdraw from this research project?

If you do consent to participate, you may withdraw at any time. If you decide to withdraw from the project, please notify a member of the research team before you withdraw. If you do withdraw, you will be asked to complete and sign a 'Withdrawal of Consent' form; this will be provided to you by the research team.

If you decide to leave the research project, the researchers will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research

project results. If you do not want your data to be included, you must tell the researchers when you withdraw from the research project.

9. Could this research project be stopped unexpectedly?

It is unlikely that this research project would be stopped unexpectedly. **10. What happens when the research project ends?**

The project is expected to end in early 2014. You can contact one of the chief investigators to get a summary of the study findings by e-mail or post.

Part 2 : How is the research project being conducted?

11. What will happen to information about me?

By signing the consent form you consent to the research team collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. All information will be de-identified before data storage. Your contact information was only needed to invite you to participate. Results may be presented at various conferences and in journal publications, but no participants will be identified. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. The data collected will be summarised in an electronic database on password protected computers which are ONLY accessible by the investigators. Hard copies of the surveys will be stored in locked cabinets and will ONLY be accessible by the investigators. Information about you may be obtained from your health records held at this and other health organisations for the purpose of this research. Any information that is obtained from your health record will also be de-identified before data storage. The hard copies of the information and the corresponding electronic database will also be stored in locked cabinets and password protected computers respectively and will ONLY be accessible by the investigators. Both the electronic databases and hard copies of the survey and any information that is obtained from your medical record will be stored for at least 7 years and then destroyed. By signing the consent form you agree to the research team accessing health records if they are relevant to your participation in this research project. In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to request access to the information about you that is collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please inform the research team member named at the end of this document if you would like to access your information.

12. Complaints

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact the researcher, Mrs Amyna Helou, or ethics committees detailed

at the end of this explanatory letter. If you become upset or distressed as a result of your participation in the research, you should contact the research team as soon as possible. The researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not members of the research team
If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a researcher participant, then you may contact Ms. Carole Branch,

Position: Administrative Officer of Mercy Health Human Research Ethics Committee

Email: cbranch@mercy.com.au

Phone: 03 8458 4808

You will need to tell Carole the name of one of the researchers given in section 1 above

13. Who is organising and funding the research?

This research project is being conducted by Mrs Amyna Helou, doctoral candidate at Monash University as part of her PhD. It is being funded by Monash University and there will not be any financial benefits arising from the conduct of this research. No member of the research team will receive a personal financial benefit from your involvement in this research project.

14. Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC).

The ethical aspects of this research project have been approved by the HREC of both the Mercy Hospital for Women and Monash University.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

15. Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the researcher on 99039025 or any of the following people:

If you would like to contact the researchers about any part of this project please contact:	If you have a complaint concerning the manner in which this research is being conducted, please contact either the Monash University Human Research Ethics Committee or the Mercy Health Research Ethics Committee:
Dr Johnson George Ph: +61 3 99039178 Email: Johnson.george@monash.edu Mrs Amyna Helou Ph: +61 3 99039025 M: +614 221 14 172 Email: amyna.helou@monash.edu	Executive officer Monash University Human Research Ethics Committee (MUHREC) Tel: +61 3 9905 2052 E-mail: muhrec@adm.monash.edu.au Mercy Health Human Research Ethics Committee Tel: +61 3 8458 4808 E-mail: ethics@mercy.com.au

We greatly look forward to hearing from you.

Yours Sincerely,

Amyna Helou

(On behalf of Dr. Johnson George, A/Prof Kay Stewart, A/Prof Kath Ryan and Prof Sue Walker)

Consent Form

Title: Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women

Principal investigator: Dr Johnson George

Associate investigators: A/Prof Kay Stewart, A/Prof Kath Ryan, Prof Sue Walker and Mrs Amyna Helou

Site: Mercy Hospital for Women

NOTE: *This consent form will remain with the Monash University researcher for their records*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

AND

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future care.

AND

I understand the purposes, procedures and risks of the research described in the project.

AND

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

AND

I understand the research team consisting of, Dr. Johnson George, Assoc/Prof Kay Stewart, Assoc/Prof Kath Ryan, Prof Sue Walker and Amyna Helou will have access to all the details I provide.

AND

I understand that the data collected from the survey will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected and both will only be accessible by the research team.

AND

I consent to the Mercy Health Human Research Ethics Committee which approved this study to access my information, or to contact me to ask about my research experience, in order to ensure that the project is being run in accordance with government standards.

Results of the study will be provided upon your request.

I, _____ (full name of participant) of

_____ (address of participant)

have read and understood the enclosed participant information form for the project titled "Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women"

Participants' name (printed) _____

Participant's signature _____ Date_____

Telephone number:

Declaration by researcher

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Researcher (printed) _____

Researcher's signature _____ Date_____

Appendix 8 – Patient Information and Consent Form interviews only Mercy Hospital for Women (Chapters 4-6)

Mercy Health
Core first

MONASH University

Participant explanatory statement and consent form

Full Project Title: Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women (interview)

Version 3 Dated January 4 29 2013
Site: Mercy Hospital for Women

Principal Researcher: Dr Johnson George

Associate Researchers: A/Prof Kay Stewart, A/Prof Kath Ryan, Prof Susan Walker, Amyna Helou

This Participant explanatory statement and consent form contains SEVEN (7) pages. Please ensure you have all the pages

Part 1 What does my participation involve?

1. Introduction

You are invited to participate in this study because you have been prescribed an anti-hypertensive medication and indicated in the hospital privacy consent form that you are willing to be contacted for research purposes. It is hoped that your involvement will help improve the management of hypertension during pregnancy. Your contribution will also aid future research.

Please read this information leaflet carefully. Please do not hesitate to ask any questions about the information in this document. You may also want to discuss the information with a relative, friend or local health worker. Please feel free to do this.

Once you have understood the project information and if you agree to take part in the project, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you have read and understand the information and that you agree to participate in the research project

You will be given a copy of the Participant explanatory statement and consent form to keep for your records.

2. What is the purpose of this research?

Hypertension in pregnancy is a condition that affects 10% of pregnancies in Australia. Unfortunately, there is no information on the management of hypertension in pregnancy from the patient's perspective and how this influences behaviours and attitudes towards medication. It is hoped that by sharing your

experiences, you will help to provide other women with support and informative data. We plan to interview 30-50 women. The results of this research will also be used to assist Amyna Helou to obtain her PhD titled 'Adherence of pregnant women to anti-hypertensive medication'.

3. What does participation in this research involve?

Your participation in this study will only begin once you have read this Participant Information leaflet and signed the consent form. You have been invited to take part in an interview based on your preference at the end of the survey which you have recently completed. Contribution to this project will involve a single one-on-one interview which can be conducted when you attend your next appointment at the Mercy Hospital for Women, Heidelberg. You can choose to have your interview conducted over the phone at your preferred time if this option does not suit you. The interview will be simple and straightforward and run for approximately 45 minutes. The questions will surround the topic of medication use and hypertension management. This interview will be the only commitment of time required by you for this project. The interview will be audio-recorded and transcribed verbatim. The researcher may also supplement the recording with hand-written notes during the interview so that we do not miss anything.

4 Other relevant information about the research project

The overall number of women participating in this study is 30-50 across two hospitals, Mercy Hospital for Women and Royal Women's Hospital. Approximately half of the participants will be from the Mercy Hospital for Women. This project involves researchers from Monash University, the Mercy Hospital for Women and the Mother and Child Health Research Centre, La Trobe University. These interviews are an extension of the questionnaire (Treatment of High Blood Pressure During Pregnancy-Beliefs, experiences ,attitudes and behaviours of pregnant women – a questionnaire) that you have recently completed and allows for further discussion of the issues that you raised.

5 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Before you make your decision, a member of the research team will be available to answer any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine care for the remainder of your pregnancy nor of any future pregnancy, your relationship with professional staff or your relationship with the Mercy Hospital for Women

6 What are the possible benefits of taking part?

We cannot guarantee or promise that the information obtained in this study will directly benefit you but it is hoped to help women like you in the near future regarding the use of blood pressure medications

during pregnancy. It is also hoped that the data collected from this study will help inform health professionals of your concerns and optimise management of hypertension during pregnancy

7 What are the possible risks and disadvantages of taking part?

There are no foreseeable risks associated with participation in this study. The interview is simple and we will not be asking any sensitive or intrusive questions. Your identity will remain anonymous in any publication resulting from the study.
At no stage of the interview are you obliged to answer any question and you may withdraw or leave the interview at any time. There is no right or wrong answer. There will be no consequences for not answering any given question. If during the interview it becomes evident that there is a concern with your blood pressure management, we will, with your permission, contact the treating team/doctor to advise them of this.

8 What if I withdraw from this research project?

If you do consent to participate, you may withdraw at any time. If you decide to withdraw from the project, please notify a member of the research team before you withdraw. If you do withdraw, you will be asked to complete and sign a 'Withdrawal of Consent' form; this will be provided to you by the research team.
If you decide to leave the research project, the researchers will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results. If you do not want your data to be included, you must tell the researchers when you withdraw from the research project

9. Could this research project be stopped unexpectedly?

It is unlikely that this research project would be stopped unexpectedly.

10. What happens when the research project ends?

The project is expected to end in early 2014. You can contact one of the chief investigators to get a summary of the study findings by e-mail or post.

Part 2. How is the research project being conducted?

11. What will happen to information about me?

By signing the consent form you consent to the research team collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. All identifiable information will be de-identified before data storage. Your contact information was only needed to invite you to participate. Results may be presented at various conferences and in journal publications, but no participants will be identified. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. The interview will audio-recorded and supplemented with hand-written notes so that we do not miss any information that you have provided during the interview. Both will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies on password protected computers; both will ONLY be accessible by the investigators. Information about you may be obtained from your health records held at this and other

health organisations for the purpose of this research. By signing the consent form you agree to the research team accessing health records if they are relevant to your participation in this research project. In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to request access to the information about you that is collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please inform the research team member named at the end of this document if you would like to access your information.

12. Complaints

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact the researcher, Mrs Amyna Helou, or ethics committees detailed at the end of this explanatory letter. If you become upset or distressed as a result of your participation in the research, you should contact the research team as soon as possible. The researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not members of the research team

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a researcher participant, then you may contact Ms. Carole Branch,
Position: Administrative Officer of Mercy Health Human Research Ethics Committee
Email: cbranch@mercy.com.au
Phone: 03 8458 4808

You will need to tell Carole the name of one of the researchers given in section 1 above

13 Who is organising and funding the research?

This research project is being conducted by Mrs Amyna Helou, doctoral candidate at Monash University as part of her PhD. It is being funded by Monash University and there will not be any financial benefits arising from the conduct of this research. No member of the research team will receive a personal financial benefit from your involvement in this research project.

14 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC).

The ethical aspects of this research project have been approved by the HREC of both the Mercy Hospital for Women and Monash University.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

15 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the researcher on 99039025 or any of the following people:

If you would like to contact the researchers about any part of this project please contact:	If you have a complaint concerning the manner in which this research is being conducted, please contact either the Monash University Human Research Ethics Committee or the Mercy Health Research Ethics Committee:
Dr Johnson George Ph: +61 3 99039178 Email: Johnson.george@monash.edu Mrs Amyna Helou Ph: +61 3 99039025 M: +614 221 14 172 Email: amyna.helou@monash.edu	Executive officer Monash University Human Research Ethics Committee (MUHREC) Tel: +61 3 9905 2052 E-mail:muhrec@adm.monash.edu.au Mercy Health Human Research Ethics Committee Tel: +61 3 8458 4808 E-mail: ethics@mercy.com.au

We greatly look forward to hearing from you.

Yours Sincerely,
Amyna Helou

(On behalf of Dr. Johnson George, A/Prof Kay Stewart, A/Prof Kath Ryan and Prof Sue Walker)

MONASH University

Mercy Health
Care first

Consent Form

Title: Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women- interview

Principal investigator: Dr Johnson George

Associate investigators: A/Prof Kay Stewart, A/Prof Kath Ryan, Prof Sue Walker and Mrs Amyna Helou

Site: Mercy Hospital for Women

***NOTE:** This consent form will remain with the Monash University researcher for their records*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

AND

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future care.

AND

I understand the purposes, procedures and risks of the research described in the project.

AND

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

AND

I understand the research team, consisting of Dr. Johnson George, Assoc/Prof Kay Stewart, Assoc/Prof Kath Ryan, Prof Sue Walker and Amyna Helou will have access to all the details I provide.

AND

I understand that the interview will be tape recorded.

AND

I understand that any data that the researcher extracts from the interview for use in reports or published findings will be fully de-identified.

AND

I understand that the data collected from the interview will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected and both will only be accessible by the research team.

AND

I consent to the Mercy Health Human Research Ethics Committee which approved this study to access my information, or to contact me to ask about my research experience, in order to ensure that the project is being run in accordance with government standards.

Results of the study will be provided upon your request.

I, _____ (full name of participant) of

_____ (address of participant)

have read and understood the enclosed participant information form for the project titled "Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women-interview"

Participants' name (printed) _____

Participant's signature _____ Date_____

Declaration by researcher

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Researcher (printed) _____

Researcher's signature _____ Date_____

Appendix 9 – Survey Mercy Hospital for Women (Phase 2 – Chapter 4)

Appendix four (4)

Mercy Health
Care first

MONASH University

Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women – a survey of outpatients

Section 1: This section has some general questions about you. Please write in the spaces provided or tick the appropriate boxes

1. What is your age? _____ years

2. Where were you born? Country _____

3. What is your ancestry? (e.g. Chinese, Indian, Maori. Provide more than one ancestry if applicable)

   ☐ Aboriginal or Torres Strait Islander

   ☐ Other (please specify) _____

4. Can you speak English? Yes ☐ No ☐

5. Please state ANY other language(s) you speak at home

_____

6. What is your highest level of education?

☐ No formal schooling

☐ Primary school

☐ High school

☐ Secondary school

☐ Technical or further educational institution (including TAFE Colleges)

☐ University education

Appendix four (4)

7. How many children do you have? (do not include the one(s) from your current pregnancy)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ more than 3 (specify) ____

8. Have you ever been a smoker? ☐ Yes ☐ No

9. Are you currently a smoker? ☐ Yes ☐ No

10. Are you a concession card holder? ☐ Yes ☐ No

Section 2: This section has some questions about your hypertension, medication, general health and health behaviours. Please write in the spaces provided or tick the appropriate boxes

11. When was your hypertension first diagnosed (if before pregnancy; state age, if during pregnancy; state gestational week)?

_____

_____

12. How would you rate your blood pressure control during the past 4 weeks?

☐ Not controlled at all ☐ Poorly controlled ☐ Somewhat controlled ☐ Well controlled

☐ Completely controlled

13. Have you had any ongoing health conditions OTHER THAN hypertension during pregnancy (please include chronic conditions that you had even before becoming pregnant and pregnancy induced conditions such as gestational diabetes, asthma etc.)?

☐ Yes (specify the condition(s) and the trimester(s))

_____

_____

_____

☐ No

Appendix four (4)

14. What medications are you currently taking for hypertension? Also mention the name of the blood pressure medication you were taking before you were pregnant (if applicable).

_____
_____

_____

15. Please list ALL other medications you are currently taking (including tablets, liquids, puffers, injections, eye drops, vitamins, herbal supplements etc.)

_____
_____
_____
_____

16. Have there been any changes in your medicines since you became pregnant?

☐ Yes (specify the changes)

_____

_____

☐ No

For each of the following statements, please tick the box that best applies to you:

17. I have strict routines for using my medications

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

18. I ensure I have enough medications so that I do not run out

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

19. I strive to follow the instructions of my doctors

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

20. I get confused about my medications

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

21. I make changes in the recommended medication management to suit my lifestyle

Appendix four (4)

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

22. I vary my recommended medication management based on how I am feeling

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

23. I put up with my medical problems before taking any action

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

End of survey

Thank you for taking the time to complete this survey

If you are interested in participating in an interview to further discuss the questions/ statements above, please provide the following details:

Name:_____

Address:_____

Email:_____

Phone no:_____

Please tick (✓) the preferred option:

☐ I would like the interview to be held face-to-face at The Mercy Hospital for Women, Heidelberg at my next appointment or at my convenience

☐ I would like a phone interview

Appendix 10 – Interview topic guide Mercy Hospital for Women (Phase 2 – Chapters 5 & 6)

Appendix 6 : Interview topic guide

Interview topic guide (in-depth interviews)

Title: Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women - interview

Three topics will be discussed:

Topic one: Their hypertension

This topic will explore the women's health beliefs surrounding their diagnosis with hypertension. When it was diagnosed and how they felt about it will be explored. Exploration into their beliefs of causation may also occur.

Topic two: Anti-hypertensive medication use during pregnancy

This topic will explore the concerns and experiences associated with the safety of using their specific anti-hypertensive medications during pregnancy and their thoughts on the importance of continuing them through pregnancy. This topic will also investigate whether there was decreased or increased use of any particular medication and why, and factors contributing to compliance. This topic will also ask participants to compare the use of blood pressure medications to other medications during pregnancy.

Topic three: Medication beliefs

This topic will explore the women's general medication beliefs related the use of other medications during the current pregnancy including over-the-counter medications, vitamins and alternative therapies, their perceived safety and benefits

Appendix 11 – Data collection form Mercy Hospital for Women (Phase 2 – Chapter 7)

DATA COLLECTION FORM

Patient ID _____

SECTION A: Maternal Data

Maternal Demographics

Age	
Weight	
BMI	
Smoking status	

Maternal Medical History

Pre-existing medical conditions (including hypertension; time of diagnosis; duration of therapy)	
Current medications - Change of antihypertensive prior to/during pregnancy - Aspirin/calcium	
Family history of pregnancy induced hypertension (first degree relatives)	

Details of current pregnancy

Parity and Gravidity	
Single ☐	Multiple pregnancy ☐
History of hypertension in previous pregnancy	
Presence of other pregnancy complications (uteroplacental vasculopathy, placental abruption, IUGR, fetal distress)	

Details of previous pregnancy (ies)

History of hypertension in previous pregnancy	Yes ☐ No ☐
Presence of other pregnancy complications (uteroplacental vasculopathy: placental abruption, IUGR, fetal distress)	
Past number of caesarean deliveries	
Past number of normal deliveries	

SECTION B: Neonatal Data

Livebirth	Yes ☐ No ☐
Gestational age at delivery	
Birthweight	
Apgar score	
Gender	
Presence of congenital abnormalities	Yes ☐ No ☐ If Yes:
NICU/SCN admission	Yes ☐ No ☐ If Yes:

SECTION C: HYPERTENSION

BP recordings and correlation with medication prescribed

Date	Gestational week	BP reading (mmHg)	Measurement method	Medication and dose prescribed	Reason for changing medication

Diagnosis of hypertension

Reading at which hypertension was diagnosed	
Gestational week of diagnosis	
Initial subtype of HDP	
Subsequent subtype of HDP	
Measures used to diagnose pre-eclampsia (proteinuria, uric acid, LFTs)	

Management of hypertension

Reading at which anti-hypertensive medication was initiated	
Target BP	
Initial medication prescribed	
Initial prescriber	Obstetrician ☐ Registrar ☐ Physician ☐ GP ☐
Initial model of care	
Other prescribers involved in the management of high BP	Obstetrician ☐ Registrar ☐ Physician ☐ GP ☐

Other relevant lab data during the pregnancy (e.g. proteinuria, LFT's, platelets)

Appendix 12 – The Royal Women's Hospital Human Research Ethics Committee approval letter (Phase 2 – Chapters 4-7)

Mr Arthur Hui
Administrative Officer
Research and Ethics Secretariat
Tel: +61 3 8345 3720
Fax: +61 3 8345 3702
Email: arthur.hui@thewomens.org.au

the women's
the royal women's hospital

ABN 62 787 822 077
Locked Bag 300
Cnr Grattan St & Flemington Rd
Parkville VIC 3052 Australia
Tel +61 3 8345 2000
www.thewomens.org.au

12.7.13

Dr J George
Centre for Medicine Use and Safety
Department of Pharmacy Practice, Monash University
381 Royal Parade
Parkville Vic 3052

Dear Dr George,

Re: Project 13/18 - Treatment of high blood pressure during pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women

Thank you for submitting the clarification and amendments as requested by the RWH Human Research Ethics Committee.

I confirm the project is now approved.

Enclosed please find Project Approval and Notification of Project Commencement Forms for your record.

Prior to commencement of your project, you are reminded that you must contact the relevant RWH Divisional Directors / Department Heads to confirm your actual commencement date. Failure to inform these RWH personnel may jeopardise their approval and support for your project.

Please return the completed Notification of Project Commencement Form to me when the project begins.

Yours sincerely,

A. C. B. Hui
Administrative Officer
Research and Ethics Secretariat

Encl:

cc Mrs L Wolke

THE ROYAL WOMEN'S HOSPITAL

RESEARCH AND HUMAN RESEARCH ETHICS COMMITTEES

PROJECT APPROVAL

PROJECT NO:	**13/18**
PROJECT TITLE:	Treatment of high blood pressure during pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women
INVESTIGATOR (S):	J George, K Stewart, A Helou, S Walker, K Ryan, F Cullinane, L Wolke
DATE OF APPROVAL:	12 July 2013
DURATION:	Thirty six (36) months

SIGNED ……
Secretary, Research & Human Research Ethics Committees **DATE**

CONDITIONS OF APPROVAL

The Principal Investigator is reminded of the following:-

1. ***Prior to commencement of the project, you must contact the relevant RWH Divisional Directors / Department Heads to confirm your actual commencement date. Failure to inform these RWH personnel may jeopardise their approval and support for your project.***
2. ***A Project may commence once the Principal Investigator has received written confirmation that the Human Research Ethics Committee has approved the Project.***
3. ***Substantial changes in protocols must be submitted to the Research/Human Research Ethics Committees for approval.***
4. ***Progress reports must be submitted annually. A request will be forwarded to the Principal Investigator. If no report is supplied, permission to continue the project may lapse.***
5. ***The Research/Human Research Ethics Committees must be notified IMMEDIATELY of any untoward or unexpected complications or side affects arising during the project or of any ethical or medico-legal problems that may arise.***
6. ***Consent forms must be available for audit and retained on file for five (5) years.***
7. ***Raw data and details of analysis must be retained by the Principal Investigator for five (5) years.***
8. ***Principal Investigator MUST upon leaving the Institution, inform the Human Research Ethics Committee as to the nominated person to replace him/her.***

PLEASE QUOTE PROJECT NO. AND TITLE FOR ALL CORRESPONDENCE

RWH PROJECT NUMBER **13/18**

THE ROYAL WOMEN'S HOSPITAL

RESEARCH AND HUMAN RESEARCH ETHICS COMMITTEES

NOTIFICATION OF PROJECT COMMENCEMENT

PROJECT TITLE:	Treatment of high blood pressure during pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women
INVESTIGATOR (S):	J George, K Stewart, A Helou, S Walker, K Ryan, F Cullinane, L Wolke
DATE OF APPROVAL:	12 July 2013
DURATION:	Thirty six (36) months

DATE OF COMMENCEMENT ……...../……...../….....

PRINCIPAL INVESTIGATOR:

NAME.....
(PLEASE PRINT)

SIGNATURE..... **DATE**……...../…….../.....

Appendix 13 – Patient Information and Consent Form whole project Royal Women's Hospital (Phase 2 – Chapters 4-7)

Appendix 1: PICF for 'Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women'

Participant explanatory statement and consent form

Full Project Title: Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women

Version 1 Dated April 27 2013

Site: The Royal Women's Hospital

Principal Researcher: Dr Johnson George

Associate Researchers: A/Prof Kay Stewart, Prof Susan Walker, A/Prof Kath Ryan, Dr Fiona Cullinane, Lisa Wolke and Amyna Helou

This 'Participant explanatory statement and consent form' contains NINE (9) pages. Please ensure you have all the pages

Part 1 What does my participation involve?

1. Introduction

You are invited to participate in this study because you have been prescribed an anti-hypertensive medication. It is hoped that your involvement will help improve the management of hypertension during pregnancy. Your contribution will also aid future research.

Please read this information leaflet carefully. Please do not hesitate to ask any questions about the information in this document. You may also want to discuss the information with a relative, friend or local health worker. Please feel free to do this.

Once you have understood the project information and if you agree to take part in the project, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you have read and understand the information and that you agree to participate in the research project

You will be given a copy of the 'Participant explanatory statement and consent form' to keep for your records.

2. What is the purpose of this research?

Hypertension is a condition that affects around 10% of pregnancies in Australia. Unfortunately, there is no information on the management of hypertension in pregnancy from the patient's perspective and how this influences behaviours and attitudes towards medication. It is hoped that by sharing your experiences, you will help to provide other women with support and informative data. The results of this research will also be used to assist Amyna Helou to obtain her PhD titled 'Adherence of pregnant women to anti-hypertensive medication'.

3. What does participation in this research involve?

Your participation in this study will only begin once you have read this Participant Information leaflet and signed the consent form. Participation in this study involves you completing a questionnaire. The questionnaire will seek information about yourself, your hypertension and your medication. It may take approximately 10 minutes for you to complete the questionnaire. You can complete the questionnaire when you are in the waiting area of the out-patient department or at home. Please leave the completed survey in the box provided or return it in the reply-paid envelope supplied. Information relating to your progress during the rest of the pregnancy and neonatal outcomes will also be collected for the purpose of this study.

You may decide not to answer some or all of the questions.

After completing the questionnaire, you may be invited to participate in a one-to-one interview around the same topic as this survey.

The decision to take part in this more in-depth interview is entirely up to you. You will be asked to sign another consent form for this part of the research if you do decide to take part in the one-to-one interview

You will not be paid for your participation in this research.

4. Other relevant information about the research project

The overall number of women participating in this study is 100 across two hospitals, the Royal Women's Hospital and Mercy Hospital for Women. Approximately half of the participants will be from the Royal Women's Hospital . This project involves researchers from Monash University, the Royal Women's Hospital, the Mercy Hospital for Women and the Mother and Child Health Research Centre, La Trobe University.

5. Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Before you make your decision, a member of the research team will be available to answer any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether or not to take part, or to take part and then withdraw, will not affect your routine care for the remainder of your pregnancy nor for any future pregnancy, your relationship with professional staff or your relationship with the Royal Women's Hospital.

6 What are the possible benefits of taking part?

We cannot guarantee or promise that the information obtained in this study will directly benefit you but it is hoped to help women like you in the near future regarding the use of blood pressure medications during pregnancy. It is also hoped that the data collected from this study will help inform health professionals of your concerns and optimise management of hypertension during pregnancy. If during this research it becomes evident that there is a concern with your blood pressure management, we will, with your permission, contact the treating team/doctor to advise them of this.

7 What are the possible risks and disadvantages of taking part?

There are no foreseeable risks associated with participation in this study. The survey is straightforward and we will not be asking any sensitive or intrusive questions. Your identity will remain anonymous in any publication resulting from the study.

At no stage of the survey are you obliged to answer any question and you may withdraw from completing the survey at any time. There is no right or wrong answer. There will be no consequences for not answering any given question.

8 What if I withdraw from this research project?

If you do consent to participate, you may withdraw at any time. If you decide to withdraw from the project, please notify a member of the research team before you withdraw. If you do withdraw, you will be asked to complete and sign a 'Withdrawal of Consent' form; this will be provided to you by the research team.

If you decide to leave the research project, the researchers will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research

project results. If you do not want your data to be included, you must tell the researchers when you withdraw from the research project.

9. Could this research project be stopped unexpectedly?

It is unlikely that this research project would be stopped unexpectedly.

10. What happens when the research project ends?

The project is expected to end in early 2014. You can contact one of the chief investigators to get a summary of the study findings by e-mail or post.

Part 2 : How is the research project being conducted?

11. What will happen to information about me?

By signing the consent form you consent to the research team collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. All information will be de-identified before data storage. Your contact information was only needed to invite you to participate. Results may be presented at various conferences and in journal publications, but no participants will be identified. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. The data collected will be summarised in an electronic database on password protected computers which are ONLY accessible by the investigators. Hard copies of the surveys will be stored in locked cabinets and will ONLY be accessible by the investigators. Information about you may be obtained from your health records held at this and other health organisations for the purpose of this research. Any information that is obtained from your health record will also be de-identified before data storage. The hard copies of the information and the corresponding electronic database will also be stored in locked cabinets and password protected computers respectively and will ONLY be accessible by the investigators. Both the electronic databases and hard copies of the survey and any information that is obtained from your medical record will be stored for at least 7 years and then destroyed. By signing the consent form you agree to the research team accessing health records if they are relevant to your participation in this research project. In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to request access to the information about you that is collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please inform the research team member named at the end of this document if you would like to access your information.

12. Complaints

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact the researcher, Mrs Amyna Helou, or ethics committees detailed at the end of this explanatory letter. If you become upset or distressed as a result of your participation in the research, you should contact the research team as soon as possible. The researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not members of the research team.
If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a researcher participant, then you may contact:

Research & Ethics Secretariat, The Royal Women's Hospital Human Research Ethics Committee

Email: research.ethics@thewomens.org.au

Telephone: (03) 8345 3720

You will need to tell the Secretariat the name of one of the researchers given in section 1 above

13. Who is organising and funding the research?

This research project is being conducted by Mrs Amyna Helou, doctoral candidate at Monash University as part of her PhD. It is being funded by Monash University and there will not be any financial benefits arising from the conduct of this research. No member of the research team will receive a personal financial benefit from your involvement in this research project.

14. Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC).

The ethical aspects of this research project have been approved by the HREC of the Royal Women's Hospital, Mercy Hospital for Women and Monash University.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

15. Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the researcher on 99039025 or any of the following people:

If you would like to contact the researchers about any part of this project please contact:	If you have a complaint concerning the manner in which this research is being conducted, please contact either the Monash University Human Research Ethics Committee or the Royal Women's Research Ethics Committee:
Dr Johnson George Ph: +61 3 99039178 Email: Johnson.george@monash.edu Mrs Amyna Helou Ph: +61 3 99039025 M: +614 221 14 172 Email: amyna.helou@monash.edu	Executive officer Monash University Human Research Ethics Committee (MUHREC) Tel: +61 3 9905 2052 E-mail: muhrec@adm.monash.edu.au Research & Ethics Secretariat The Royal Women's Hospital Human Research Ethics Committee Email: research.ethics@thewomens.org.au Telephone: (03) 8345 3720

We greatly look forward to hearing from you.

Yours Sincerely,

Amyna Helou

(On behalf of Dr. Johnson George, A/Prof Kay Stewart, A/Prof Kath Ryan, Dr Fiona Cullinane, Lisa Wolke and Prof Sue Walker)

Consent Form

Title: Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women

Principal investigator: Dr Johnson George

Associate investigators: A/Prof Kay Stewart, A/Prof Kath Ryan, Prof Sue Walker, Dr Fiona Cullinane and Mrs Amyna Helou

Site: The Royal Women's Hospital

NOTE: *This consent form will remain with the Monash University researcher for their records*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

AND

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future care.

AND

I understand the purposes, procedures and risks of the research described in the project.

AND

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

AND

I understand the research team consisting of, Dr. Johnson George, Assoc/Prof Kay Stewart, Assoc/Prof Kath Ryan, Prof Sue Walker, Dr Fiona Cullinane, Lisa Wolke and Amyna Helou will have access to all the details I provide.

AND

I understand that the data collected from the survey will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected and both will only be accessible by the research team.

AND

I consent to the Royal Women's Human Research Ethics Committee which approved this study to access my information, or to contact me to ask about my research experience, in order to ensure that the project is being run in accordance with government standards.

Results of the study will be provided upon your request.

I, _____ (full name of participant) of

_____ (address of participant)

have read and understood the enclosed participant information form for the project titled "Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women"

Participants' name (printed) _____

Participant's signature _____ Date_____

Telephone number:

Declaration by researcher

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Researcher (printed) _____

Researcher's signature _____ Date_____

Appendix 14 – Patient Information and Consent Form interviews only Royal Women's Hospital (Phase 2 – Chapters 4-6)

Appendix 2: PICF for in-depth interviews

Participant explanatory statement and consent form

Full Project Title: Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women (interview)

Version 1 Dated April 27 2013
Site: The Royal Women's Hospital

Principal Researcher: Dr Johnson George

Associate Researchers: A/Prof Kay Stewart, A/Prof Kath Ryan, Dr Fiona Cullinane, Lisa Wolke, Prof Susan Walker, Amyna Helou

This Participant explanatory statement and consent form contains SEVEN (7) pages. Please ensure you have all the pages

Part 1 What does my participation involve?

1. Introduction

You are invited to participate in this study because you have been prescribed an anti-hypertensive medication. It is hoped that your involvement will help improve the management of hypertension during pregnancy. Your contribution will also aid future research.

Please read this information leaflet carefully. Please do not hesitate to ask any questions about the information in this document. You may also want to discuss the information with a relative, friend or local health worker. Please feel free to do this.

Once you have understood the project information and if you agree to take part in the project, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you have read and understand the information and that you agree to participate in the research project

You will be given a copy of the Participant explanatory statement and consent form to keep for your records.

2. What is the purpose of this research?

Hypertension in pregnancy is a condition that affects 10% of pregnancies in Australia. Unfortunately, there is no information on the management of hypertension in pregnancy from the patient's perspective and how this influences behaviours and attitudes towards medication. It is hoped that by sharing your

experiences, you will help to provide other women with support and informative data. We plan to interview 30-50 women. The results of this research will also be used to assist Amyna Helou to obtain her PhD titled 'Adherence of pregnant women to anti-hypertensive medication'.

3. What does participation in this research involve?

Your participation in this study will only begin once you have read this Participant Information leaflet and signed the consent form. You have been invited to take part in an interview based on your preference at the end of the survey which you have recently completed. Contribution to this project will involve a single one-on-one interview which can be conducted when you attend your next appointment at the Royal Women's Hospital, Parkville. You can choose to have your interview conducted over the phone at your preferred time if this option does not suit you. The interview will be simple and straightforward and run for approximately 45 minutes. The questions will surround the topic of medication use and hypertension management. This interview will be the only commitment of time required by you for this project. The interview will be audio-recorded and transcribed verbatim. The researcher may also supplement the recording with hand-written notes during the interview so that we do not miss anything.

4 Other relevant information about the research project

The overall number of women participating in this study is 30-50 across two hospitals, The Royal Women's Hospital and Mercy Hospital for Women. Approximately half of the participants will be from the Royal Women's Hospital. This project involves researchers from Monash University, The Royal Women's Hospital, the Mercy Hospital for Women and the Mother and Child Health Research Centre, La Trobe University. These interviews are an extension of the questionnaire (Treatment of High Blood Pressure During Pregnancy-Beliefs, experiences ,attitudes and behaviours of pregnant women – a questionnaire) that you have recently completed and allows for further discussion of the issues that you raised.

5 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Before you make your decision, a member of the research team will be available to answer any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine care for the remainder of your pregnancy nor of any future pregnancy, your relationship with professional staff or your relationship with The Royal Women's Hospital.

6 What are the possible benefits of taking part?

We cannot guarantee or promise that the information obtained in this study will directly benefit you but it is hoped to help women like you in the near future regarding the use of blood pressure medications during pregnancy. It is also hoped that the data collected from this study will help inform health professionals of your concerns and optimise management of hypertension during pregnancy

7 What are the possible risks and disadvantages of taking part?

There are no foreseeable risks associated with participation in this study. The interview is simple and we will not be asking any sensitive or intrusive questions. Your identity will remain anonymous in any publication resulting from the study.
At no stage of the interview are you obliged to answer any question and you may withdraw or leave the interview at any time. There is no right or wrong answer. There will be no consequences for not answering any given question. If during the interview it becomes evident that there is a concern with your blood pressure management, we will, with your permission, contact the treating team/doctor to advise them of this.

8 What if I withdraw from this research project?

If you do consent to participate, you may withdraw at any time. If you decide to withdraw from the project, please notify a member of the research team before you withdraw. If you do withdraw, you will be asked to complete and sign a 'Withdrawal of Consent' form; this will be provided to you by the research team.
If you decide to leave the research project, the researchers will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results. If you do not want your data to be included, you must tell the researchers when you withdraw from the research project

9. Could this research project be stopped unexpectedly?

It is unlikely that this research project would be stopped unexpectedly.

10. What happens when the research project ends?

The project is expected to end in early 2014. You can contact one of the chief investigators to get a summary of the study findings by e-mail or post.

Part 2. How is the research project being conducted?

11. What will happen to information about me?

By signing the consent form you consent to the research team collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. All identifiable information will be de-identified before data storage. Your contact information was only needed to invite you to participate. Results may be presented at various conferences and in journal publications, but no participants will be identified. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. The interview will audio-recorded and supplemented with

hand-written notes so that we do not miss any information that you have provided during the interview. Both will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies on password protected computers; both will ONLY be accessible by the investigators. Information about you may be obtained from your health records held at this and other health organisations for the purpose of this research. By signing the consent form you agree to the research team accessing health records if they are relevant to your participation in this research project. In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to request access to the information about you that is collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please inform the research team member named at the end of this document if you would like to access your information.

12. Complaints

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact the researcher, Mrs Amyna Helou, or ethics committees detailed at the end of this explanatory letter. If you become upset or distressed as a result of your participation in the research, you should contact the research team as soon as possible. The researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not members of the research team

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a researcher participant, then you may contact:

Research & Ethics Secretariat, The Royal Women's Hospital Human Research Ethics Committee
Email: research.ethics@thewomens.org.au
Telephone: (03) 8345 3720

You will need to tell Secretariat the name of one of the researchers given in section 1 above

13 Who is organising and funding the research?

This research project is being conducted by Mrs Amyna Helou, doctoral candidate at Monash University as part of her PhD. It is being funded by Monash University and there will not be any financial benefits arising from the conduct of this research. No member of the research team will receive a personal financial benefit from your involvement in this research project.

14 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC).

The ethical aspects of this research project have been approved by the HREC of the Royal Women's Hospital, Mercy Hospital for Women and Monash University.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

15 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the researcher on 99039025 or any of the following people:

If you would like to contact the researchers about any part of this project please contact:	If you have a complaint concerning the manner in which this research is being conducted, please contact either the Monash University Human Research Ethics Committee or the Mercy Health Research Ethics Committee:
Dr Johnson George Ph: +61 3 99039178 Email: Johnson.george@monash.edu Mrs Amyna Helou Ph: +61 3 99039025 M: +614 221 14 172 Email: amyna.helou@monash.edu	Executive officer Monash University Human Research Ethics Committee (MUHREC) Tel: +61 3 9905 2052 E-mail:muhrec@adm.monash.edu.au Research & Ethics Secretariat, The Royal Women's Hospital Human Research Ethics Committee Telephone: (03) 8345 3720 Email: research.ethics@thewomens.org.au

We greatly look forward to hearing from you.

Yours Sincerely,
Amyna Helou

(On behalf of Dr. Johnson George, A/Prof Kay Stewart, A/Prof Kath Ryan, Dr Fiona Cullinane, Lisa Wolke and Prof Sue Walker)

Consent Form

Title: Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women- interview

Principal investigator: Dr Johnson George

Associate investigators: A/Prof Kay Stewart, A/Prof Kath Ryan, Prof Sue Walker, Dr Fiona Cullinane, Lisa Wolke and Mrs Amyna Helou

Site: The Royal Women's Hospital

***NOTE:** This consent form will remain with the Monash University researcher for their records*

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

AND

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future care.

AND

I understand the purposes, procedures and risks of the research described in the project.

AND

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

AND

I understand the research team, consisting of Dr. Johnson George, Assoc/Prof Kay Stewart, Assoc/Prof Kath Ryan, Prof Sue Walker, Dr Fiona Cullinane, Lisa Wolke and Amyna Helou will have access to all the details I provide.

AND

I understand that the interview will be tape recorded.

AND

I understand that any data that the researcher extracts from the interview for use in reports or published findings will be fully de-identified.

AND

I understand that the data collected from the interview will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected and both will only be accessible by the research team.

AND

I consent to the Royal Women's Human Research Ethics Committee which approved this study to access my information, or to contact me to ask about my research experience, in order to ensure that the project is being run in accordance with government standards.

Results of the study will be provided upon your request.

I, _____ (full name of participant) of

_____ (address of participant)

have read and understood the enclosed participant information form for the project titled "Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women-interview"

Participants' name (printed) _____

Participant's signature _____ Date_____

Declaration by researcher

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Researcher (printed) _____

Researcher's signature _____ Date_____

Appendix 15 – Survey Royal Women's Hospital (Phase 2 – Chapter 4)

Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women – questionnaire

Section 1: This section has some general questions about you. Please write in the spaces provided or tick the appropriate boxes

1. What is your age? _____ years

2. Where were you born? Country _____

3. What is your ancestry? (e.g. Chinese, Indian, Maori. Provide more than one ancestry if applicable)

   ☐ Aboriginal or Torres Strait Islander

   ☐ Other (please specify) _____

4. Can you speak English? Yes ☐ No ☐

5. Please state ANY other language(s) you speak at home

_____

6. What is your highest level of education?

☐ No formal schooling

☐ Primary school

☐ High school

☐ Secondary school

☐ Technical or further educational institution (including TAFE Colleges)

☐ University education

7. How many children do you have? (do not include the one(s) from your current pregnancy)

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ more than 3 (specify) ____

8. Have you ever been a smoker? ☐ Yes ☐ No

9. Are you currently a smoker? ☐ Yes ☐ No

10. Are you a concession card holder? ☐ Yes ☐ No

Section 2: This section has some questions about your high blood pressure, medication, general health and health behaviours. Please write in the spaces provided or tick the appropriate boxes

11. When was your high blood pressure first diagnosed (if before pregnancy; state age, if during pregnancy; state gestational week)?

_____

_____

12. How would you rate your blood pressure control during the past 4 weeks?

☐ Not controlled at all ☐ Poorly controlled ☐ Somewhat controlled ☐ Well controlled

☐ Completely controlled ☐ Don't know

13. Have you had any ongoing health conditions OTHER THAN high blood pressure during pregnancy (please include chronic conditions that you had even before becoming pregnant and pregnancy induced conditions such as gestational diabetes, asthma etc.)?

☐ Yes (specify the condition(s) and the trimester(s))

_____

_____

_____

☐ No

14. What medication(s) are you currently taking for high blood pressure? Also mention the name of the blood pressure medication you were taking before you were pregnant (if applicable).

_____
_____

_____

15. Please list ALL other medications you are currently taking (including tablets, liquids, puffers, injections, eye drops, vitamins, herbal supplements etc.)

_____
_____
_____
_____

16. Have there been any changes in your medicines since you became pregnant?

☐ Yes (specify the changes)

_____

_____

☐ No

For each of the following statements, please tick the box that best applies to you with regards to your high blood pressure and use of medicines to reduce your blood pressure:

17. I have strict routines for using my medications

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

18. I ensure I have enough medications so that I do not run out

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

19. I strive to follow the instructions of my doctors

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

20. I get confused about my medications

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

21. I make changes in the recommended medication management to suit my lifestyle

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

22. I vary my recommended medication management based on how I am feeling

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

23. I put up with my medical problems before taking any action

☐ Always ☐ Often ☐ Sometimes ☐ Rarely ☐ Never

End of survey

Thank you for taking the time to complete this survey

If you are interested in participating in an interview to further discuss the questions/ statements above, please provide the following details:

Name:_____

Address:_____

Email:_____

Phone no:_____

Please tick (✓) the preferred option:

☐ I would like the interview to be held face-to-face at The Royal Women's Hospital, Parkville at my next appointment or at my convenience

☐ I would like a phone interview

Appendix 16 – Interview topic guide Royal Women's Hospital (Phase 2 – Chapters 5 & 6)

Appendix 4: Interview topic guide

Interview topic guide (in-depth interviews)

Title: Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women - interview

Three topics will be discussed:

Topic one: Their hypertension

This topic will explore the women's health beliefs surrounding their diagnosis with hypertension. When it was diagnosed and how they felt about it will be explored. Exploration into their beliefs of causation may also occur.

Topic two: Anti-hypertensive medication use during pregnancy

This topic will explore the concerns and experiences associated with the safety of using their specific anti-hypertensive medications during pregnancy and their thoughts on the importance of continuing them through pregnancy. This topic will also investigate whether there was decreased or increased use of any particular medication and why, and factors contributing to compliance. This topic will also ask participants to compare the use of blood pressure medications to other medications during pregnancy.

Topic three: Medication beliefs

This topic will explore the women's general medication beliefs related the use of other medications during the current pregnancy including over-the-counter medications, vitamins and alternative therapies, their perceived safety and benefits

Appendix 17 – Data collection form Royal Women's Hospital (Phase 2 – Chapter 7)

Appendix five

Treatment of High Blood Pressure During Pregnancy: Beliefs, experiences, attitudes and behaviours of pregnant women

Data Collection Form for Prospective Data Collection

Patient ID

SECTION A: Maternal Data

Details of current pregnancy

Parity and Gravidity	
Single ☐	Multiple pregnancy☐
Presence of other pregnancy complications (uteroplacental vasculopathy: placental abruption, IUGR, fetal distress)	
Vaginal birth ☐ Spontaneous onset of labour? Induction of labour? Indication:	Caesarean birth ☐ Indication:
Date of delivery	

Details of previous pregnancy (ies)

History of hypertension in previous pregnancy	Yes ☐ No ☐
Presence of other pregnancy complications (uteroplacental vasculopathy: placental abruption, IUGR, fetal distress)	
Past number of caesarean deliveries	
Past number of normal deliveries	

SECTION B: Neonatal Data

Livebirth	Yes ☐ No ☐
Gestational age at delivery	
Birthweight	
Apgar score	
Gender	
Presence of congenital abnormalities	Yes ☐ No ☐ If Yes:
NICU/SCN admission	Yes ☐ No ☐ If Yes:

SECTION C: HYPERTENSION

BP recordings and correlation with medication prescribed

Date	Gestational week	BP reading (mmHg)	Measurement method	Medication and dose prescribed	Reason for changing medication

Diagnosis of hypertension

Reading at which hypertension was diagnosed	
Gestational week of diagnosis	
Initial subtype of HDP	
Subsequent subtype of HDP	
Measures used to diagnose pre-eclampsia (proteinuria, uric acid, LFTs)	

Management of hypertension

Reading at which anti-hypertensive medication was initiated	
Target BP	
Initial medication prescribed	
Initial prescriber	Obstetrician ☐ Registrar ☐ Physician ☐ GP ☐
Initial model of care	
Other prescribers involved in the management of high BP	Obstetrician ☐ Registrar ☐ Physician ☐ GP ☐

Other relevant lab data during the pregnancy (e.g. proteinuria, LFT's, platelets)

Appendix 18 – Consent to release medical information Barwon Health (Phase 2 – Chapter 7)

CONSENT TO RELEASE MEDICAL INFORMATION

I……
(Given Names) (Surname)

D.O.B ……

Of ……
(Address)

hereby authorise Barwon Health to release to

……
(Name of Solicitor/Insurance/Police/Doctor/Other Person)

of……
(Address)

a report on my medical condition and treatment on/between ……
(dates)

Dated this……day of……20……..

Signed……

Witnessed by ……
(signature)

……
(printed name)

Prompt Doc No: BAH0001690 v4.0

References

1. World Health Organization. Health topics hypertension [Internet]. Geneva Switzerland [cited 2021 Feb 10]. Available from: https://www.who.int/health-topics/hypertension/#tab=tab1.

2. Australian Bureau of Statistics. Hypertension and measured high blood pressure. Contains key statistics and information about hypertension and high blood pressure prevalence in Australia, including state and territory findings 2017-2018 financial year [Internet]. Canberra ACT [cited 2021 Feb 10]. Available from: https://www.abs.gov.au/statistics/health/health-conditions-and-risks/hypertension-and-measured-high-blood-pressure/latest-release.

3. Gabb GM, Mangoni A, Anderson CS, Cowley D, Dowden JS, Golledge J, et al. Guideline for the diagnosis and management of hypertension in adults-2016. Med J Australia. 2016;205(2):85-7.

4. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017;135(10):E146-E603.

5. Hird TR, Zomer E, Owen AJ, Magliano DJ, Liew D, Ademi Z. Productivity burden of hypertension in Australia. Hypertension. 2019;73(4):777-84.

6. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton M, North RA, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. Aust N Z J Obstet Gyn. 2015;55(5):e1-e29.

7. World Health Organisation. Maternal mortality 2016 [Internet]. Geneva Switzerland.[cited 2021 Feb 11]. Available from: http://www.who.int/mediacentre/factsheets/fs348/en/.

8. von Dadelszen P, Magee LA. Preventing deaths due to the hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol. 2016;36:83-102.

9. Ukah UV, De Silva DA, Payne B, Magee LA, Hutcheon JA, Brown H, et al. Prediction of adverse maternal outcomes from pre-eclampsia and other hypertensive disorders of pregnancy: A systematic review. Pregnancy Hypertens. 2018;11:115-23.

10. Redman C and Staff A. Fetal Growth Restriction and Hypertensive Diseases of Pregnancy. Placental-Fetal Growth Restriction. Cambridge: Cambridge University Press; 2018. p. 31-43.

11. Pouta A, Hartikainen AL, Sovio U, Gissler M, Laitinen J, McCarthy MI, et al. Manifestations of metabolic syndrome after hypertensive pregnancy. Hypertension. 2004;43(4):825-31.

12. Macgilli.I, Rose GA, Rowe B. Blood Pressure Survey in Pregnancy. Clin Sci. 1969;37(2):395-444.

13. Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, et al. Less-Tight versus Tight Control of Hypertension in Pregnancy. New Engl J Med. 2015;372(5):407-17.

14. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy A meta-analysis. Obstet Gynecol. 2010;116(2):402-14.

15. Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Db Syst Rev. 2010(8).

16. Mosley AT, Witte AP. Drugs in pregnancy: Do the benefits outweigh the risks? US Pharm. 2013;38(9):43-6.

17. Bellos I, Pergialiotis V, Papapanagiotou A, Loutradis D, Daskalakis G. Comparative efficacy and safety of oral antihypertensive agents in pregnant women with chronic hypertension: A network metaanalysis. Am J Obstet Gynecol. 2020;223(4):525-37.

18. Australian Drug Evaluation Committee. Prescribing medicines in pregnancy database [Internet]. Canberra ACT. [cited 2021 Feb 11] Available from: https://www.tga.gov.au/prescribing-medicines-pregnancy-database.

19. Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Db Syst Rev. 2018(10).

20. Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists A systematic review. Hypertension. 2012;60(2):444-449.

21. Kennedy D. Labelling of drugs in pregnancy ripe for overhaul. November 2011. November 2011, https://www.ama.com.au/media/labelling-drugs-pregnancy-ripe-overhaul.

22. Brown E, Hotham E, Hotham N. Views of obstetric practitioners and hospital pharmacists on therapeutic goods administration approved product information for pregnancy and lactation. Aust N Z J Obstet Gynaecol. 2014;54(2):184-8.

23. NPS MedicineWise. Presolol (Labetalol) Consumer Medicines Information leaflet [Internet]. [cited 2021 June 16] Available from: https://www.nps.org.au/medicine-finder/presolol-tablets.

24. NPS MedicineWise. Adalat (Nifedipine) Consumer Medicines Information leaflet [Internet]. [cited 2021 Nov 25] Available from: https://www.nps.org.au/medicine-finder/adalat-tablets.

25. Food and Drug Administration. FDA Pregnancy Risk Information: An Update [Internet]. [cited 2021 Nov 23] Available from: https://www.drugs.com/pregnancy-categories.html#previous.

26. DiMatteo MR. Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. Med Care. 2004;42(3):200-9.

27. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness J Psychosom Res. 1999;47(6):555-67.

28. Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. Eur J Clin Pharmacol. 2010;66(2):207-14.

29. Butters LaH, C.A. Awareness among pregnant women of the effect on the fetus of commonly used drugs. Midwifery. 1990;6:146-54.

30. Aviv RI, Chubb K, Lindow SW. The prevalence of maternal medication ingestion in the antenatal period. S Afr Med J. 1993;83(9):657-60.

31. Nachega J. The effect of pregnancy on adherence to HAART among HIV-infected South African women: A pharmacy claims-based analysis. Trop Med Int Health. 2010;15(8):S7-S11.

32. Nielsen MJ, Norgaard M, Holland-Fisher P, Christensen LA. Self-reported antenatal adherence to medical treatment among pregnant women with Crohns' disease. Aliment Pharm Ther. 2010;32(1):49-58.

33. Julsgaard M, Norgaard M, Hvas CL, Buck D, Christensen LA. Self-reported adherence to medical treatment prior to and during pregnancy among women with ulcerative colitis. Inflamm Bowel Dis. 2011;17(7):1573-80.

34. Lim AS, Stewart K, Abramson MJ, Ryan K, George J. Asthma during Pregnancy: The experiences, concerns and views of pregnant women with asthma. J Asthma. 2012;49(5):474-9.

35. Toloza FJK, Theriot SE, Ospina NMS, Nooruddin S, Keathley B, Johnson SM, et al. Knowledge, Attitudes, Beliefs, and Treatment Burden Related to the Use of levothyroxine in hypothyroid pregnant women in the United States. Thyroid. 2021;31(4):669-77.

36. Webster LM, Reed K, Myers JE, Burns A, Gupta P, Patel P, et al. Quantifying adherence to antihypertensive medication for chronic hypertension during pregnancy. Pregnancy Hypertens. 2019;17:12-4.

37. Sabate Ee. Adherence to long-term therapies: Evidence for action. Geneva, Switzerland. World Health Organization. 2003.

38. Horne R. Representations of medications and treatment: Advances in theory and measurement. K.J. Petrie Jawe, Editor. London: Harwood Academic; 1997.

39. Wroe AL. Intentional and unintentional nonadherence: A study of decision making. J Behav Med. 2002;25(4):355-72.

40. Hugtenburg JG, Timmers L, Elders PJM, Vervloet M, van Dijk L. Definitions, variants, and causes of nonadherence with medication: A challenge for tailored interventions. Patient Prefer Adher. 2013;7:675-82.

41. George J, Mackinnon A, Kong DCM, Stewart K. Development and validation of the Beliefs and Behaviour Questionnaire (BBQ). Patient Educ Couns. 2006;64(1-3):50-60.

42. Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-reported medication adherence for routine clinical use: A systematic review. BMC Med Res Methodol. 2011;11.

43. Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, et al. Self-report measures of medication adherence behavior: Recommendations on optimal use. Transl Behav Med. 2015;5(4):470-82.

44. Kini V, Ho PM. Interventions to improve medication adherence: A review. JAMA. 2018;320(23):2461-73.

45. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24(1):67-74.

46. Vrijens B, Antoniou S, Burnier M, de la Sierra A, Volpe M. Current situation of medication adherence in hypertension. Front Pharmacol. 2017;8.

47. Osterberg L, Blaschke T. Drug therapy: Adherence to medication. New Engl J Med. 2005;353(5):487-97.

48. Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD, Mukherjee J. Can Simple Clinical measurements detect patient non-compliance. Hypertension. 1980;2(6):757-64.

49. Vest AR, Cho LS. Hypertension in pregnancy. Curr Atheroscler Rep. 2014;16(3).

50. Feldman Y, Koren G, Mattice D, Shear H, Pellegrini E, Macleod SM. Determinants of recall and recall bias in studying drug and chemical-exposure in pregnancy. Teratology. 1989;40(1):37-45.

51. Bar-Oz B, Moretti ME, Mareels G, Van Tittelboom T, Koren G. Reporting bias in retrospective ascertainment of drug-induced embryopathy. Lancet. 1999;354(9191):1700-1.

52. Bryant HE, Visser N, Love EJ. Records, Recall Loss, and Recall Bias in Pregnancy: A comparison of interview and medical records data of pregnant and postnatal women. Am J Public Health. 1989;79(1):78-80.

53. Wang PS. How well do patients report noncompliance with antihypertensive medications?: A comparison of self-report versus filled prescriptions. Pharmacoepidemiology & Drug Safety 2004;13(1):11-9.

54. Sawicki E, Stewart K, Wong S, Leung L, Paul E, George J. Medication use for chronic health conditions by pregnant women attending an Australian maternity hospital. Aust N Z J Obstet Gynaecol. 2011;51(4):333-8.

55. Simons LA, Ortiz M, Calcino G. Persistence with antihypertensive medication: Australia-wide experience, 2004-2006. Med J Aust. 2008;188(4):224-7.

56. Simons LA, Ortiz M, Calcino G. Persistence with a single pill versus two pills of amlodipine and atorvastatin: the Australian experience, 2006-2010. Med J Aust. 2011;195(3):134-7.

57. Marshall IJ, Wolfe CD, McKevitt C. Lay perspectives on hypertension and drug adherence: Systematic review of qualitative research. BMJ. 2012;345:e3953.

58. Horne R, Clatworthy J, Polmear A, Weinman J. Do hypertensive patients' beliefs about their illness and treatment influence medication adherence and quality of life? J Hum Hypertens. 2001;15:S65-S8.

59. Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. Eur J Clin Pharmacol. 2010;66(2):207-14.

60. Wang W, Xie X, Yuan T, Wang Y, Zhao F, Zhou Z, et al. Epidemiological trends of maternal hypertensive disorders of pregnancy at the global, regional, and national levels: a population-based study. BMC Pregnancy Childbirth. 2021;21(1):364.

61. Australian Institute of Health and Welfare. Maternal deaths in Australia [Internet]. Canberra: Australian Institute of Health and Welfare 2020 [cited 10 Nov 2021]. Available from: https://www.aihw.gov.au/reports/mothers-babies/maternal-deaths-in-australia

62. Gemechu KS, Assefa N, Mengistie B. Prevalence of hypertensive disorders of pregnancy and pregnancy outcomes in Sub-Saharan Africa: A systematic review and meta-analysis. Womens Health. 2020;16.

63. Li F, Qin J, Zhang S, Chen L. Prevalence of hypertensive disorders in pregnancy in China: A systematic review and meta-analysis. Pregnancy Hypertens. 2021;24:13-21.

64. Olie V, Moutengou E, Grave C, Deneux-Tharaux C, Regnault N, Kretz S, et al. Prevalence of hypertensive disorders during pregnancy in France (2010-2018): The nationwide CONCEPTION study. J Clin Hypertens (Greenwich). 2021.

65. Roberts CL, Algert CS, Morris JM, Ford JB, Henderson-Smart DJ. Hypertensive disorders in pregnancy: A population-based study. Med J Australia. 2005;182(7):332-5.

66. Thornton C, Dahlen H, Korda A, Hennessy A. The incidence of preeclampsia and eclampsia and associated maternal mortality in Australia from population-linked datasets: 2000-2008. Am J Obstet Gynecol. 2013;208(6).

67. Loerup L, Pullon RM, Birks J, Fleming S, Mackillop LH, Gerry S, et al. Trends of blood pressure and heart rate in normal pregnancies: a systematic review and meta-analysis. BMC Med. 2019;17(1).

68. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive disorders of pregnancy ISSHP classification, diagnosis, and management: Recommendations for international practice. Hypertension. 2018;72(1):24-43.

69. National Institute of Healthcare Excellence. Hypertension in pregnancy: Diagnosis and management (NG133) 1-54 2019 [Internet]. London, United Kingdom [cited 2021 Feb 11]. Available at: https://www.nice.org.uk/guidance/ng133/resources/hypertension-in-pregnancydiagnosis-and-management-pdf-66141717671365. 2019.

70. American College of Obstetricians and Gynecologists' Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol. 2019;133(1):1.

71. American College of Obstreticians and Gynecologists' Committee on Practice. Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. Obstet Gynecol. 2019;133(1):e26-e50.

72. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P, Pr CHD. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens. 2014;4(2):105-45.

73. National Heart Foundation. Guideline for the diagnosis and management of hypertension in adults – 2016. Melbourne: National Heart Foundation of Australia; 2016.

74. National Institute of Healthcare Excellence. Hypertension in adults: Diagnosis and management NICE guideline [NG136] 2019 [Internet]. London, United Kingdom. [cited 2021 Feb 12]. Available from:https://www.nice.org.uk/guidance/ng136/chapter/Recommendations#diagnosing-hypertension.

75. Hypertension Canada. Guidelines for the diagnosis, risk assessment, prevention, and treatment of hypertension 2020. [Internet] [cited 2021 Feb 13]Available from: https://guidelines.hypertension.ca/diagnosis-assessment/diagnosis/.

76. Whelton PK, Carey RM. The 2017 Clinical practice guideline for high blood pressure.JAMA. 2017;318(21):2073-4.

77. Agrawal A, Wenger NK. Hypertension During Pregnancy. Curr Hypertens Rep. 2020;22(9).

78. Lowe SA, Brown, M.A, Dekker G, Gatt S, McLintock C, McMahon L, Mangos G, Moore MP, Muller P, Paech M, Walters B. Guidelines for the management of Hypertensive Disorders of Pregnancy 2008 [Webpage]. Society of Obstetric Medicine of Australia and New Zealand. Available from: http://www.somanz.org/pdfs/somanz_guidelines_2008.pdf.

79. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy. 2001;20(1):Ix-Xiv.

80. Barry C, Fielding, R, Green P et al. for the National Collaborating Centre for Women's and Children's Health. Hypertension in pregnancy: The management of hypertensive disorders during pregnancy (NICE Clinical Guideline). London, United Kingdom: Royal College of Obstetricians and Gynaecologists; 2010 August

81. Magee L, Helewa M, Rey E et al. SOGC Clinical Practice Guideline: diagnosis, evaluation and management of the hypertensive disorders of pregnancy. JOGC. 2008;30(Suppl1):S1-S48.

82. Gifford RW, August PA, Cunningham G, Green LA, Lindheimer MD, McNellis D, et al. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000;183(1):S1-S22.

83. American College of Obstreticians and Gynecologists' Committee Opinion No. 767: Emergent Therapy for Acute-Onset, Severe Hypertension During Pregnancy and the Postpartum Period. Obstet Gynecol. 2019;133(2):e174-e80.

84. Davey DA, MacGillivray, I. The classification and definition of the hypertensive disorders of pregnancy. Am J Obstet Gynecol. 1988;158:892-8.

85. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy Hypertens. 2014;4(2):97-104.

86. Yoder SR, Thornburg LL, Bisognano JD. Hypertension in pregnancy and women of childbearing age. Am J Med. 2009;122(10):890-5.

87. Chahine KM, Sibai BM. Chronic hypertension in pregnancy: New concepts for classification and management. Am J Perinatol. 2019;36(2):161-8.

88. Ananth CV, Duzyj CM, Yadava S, Schwebel M, Tita ATN, Joseph KS. Changes in the prevalence of chronic hypertension in pregnancy, United States, 1970 to 2010. Hypertension. 2019;74(5):1089-95.

89. Seely EW, Ecker J. Chronic Hypertension in Pregnancy. Circulation. 2014;129(11):1254-61.

90. Sibai BM, Abdella TN, Anderson GD. Pregnancy outcome in 211 patients with mild chronic hypertension. Obstet Gynecol. 1983;61(5):571-6.

91. Malha L, August P. Secondary Hypertension in Pregnancy. Curr Hypertens Rep. 2015;17(7).

92. Bateman BT, Bansil P, Hernandez-Diaz S, Mhyre JM, Callaghan WM, Kuklina EV. Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. Am J Obstet Gynecol. 2012;206(2).

93. Johnson S, Liu B, Kalafat E, Thilaganathan B, Khalil A. Maternal and Perinatal Outcomes of White Coat Hypertension During Pregnancy: A systematic review and meta-Analysis. Hypertension. 2020;76(1):157-66.

94. Brown MA, Robinson A, Jones M. The white coat effect in hypertensive pregnancy: much ado about nothing? BJOG. 1999;106(5):474-80.

95. Salazar MR, Espeche WG, Balbin E, Sisnieguez CEL, Sisnieguez BCL, Stavile RN, et al. Office blood pressure values and the necessity of out-of-office measurements in high-risk pregnancies. J Hypertens. 2019;37(9):1838-44.

96. Brown MA, Mangos G, Davis G, Homer C. The natural history of white coat hypertension during pregnancy. BJOG. 2005;112(5):601-6.

97. Rodrigues A, Barata C, Marques I, Almeida MC. Diagnosis of white coat hypertension and pregnancy outcomes. Pregnancy Hypertens. 2018;14:121-4.

98. Matthys LA, Coppage KH, Lambers DS, Barton JR, Sibai BM. Delayed postpartum preclampsia: An experience of 151 cases. Am J Obstet Gynecol. 2004;190(5):1464-6.

99. Saudan P, Brown, M.A, Buddle M.L, Jones, M. Does gestational hypertension become pre-eclampsia? BJOG. 1998;105:1177-84.

100. World Health Organization. Trends in maternal mortality: 1990 to 2015. Estimates by WHO, UNICEF, UNFPA, The World Bank and the United Nations Population Division. 2015. [Internet]. [2021 May 12] Available from: http://apps.who.int/iris/bitstream/10665/194254/1/9789241565141_eng.pdf?ua=1

101. Chappell L, Cluver C, Kingdom J and Tong S. Pre-eclampsia. [Online first]. The Lancet 2021 Jul 24;398(10297):341-354.

102. Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. Br Med J. 2019;366.

103. Umesawa M, Kobashi G. Epidemiology of hypertensive disorders in pregnancy: Prevalence, risk factors, predictors and prognosis. Hypertens Res. 2017;40(3):213-20.

104. Auger N, Luo ZC, Nuyt AM, Kaufman JS, Naimi AI, Platt RW, et al. Secular trends in preeclampsia incidence and outcomes in a large canada database: A longitudinal study over 24 years. Can J Cardiol. 2016;32(8):987 e15-23.

105. Bell MJ. A historical overview of preeclampsia-eclampsia. J Obstet Gynecol Neonatal Nurs. 2010;39(5):510-8.

106. Reddy M, Fenn S, Rolnik DL, Mol B, Costa FD, Wallace EM, et al. The impact of the definition of preeclampsia on disease diagnosis and outcomes: a retrospective cohort study. Am J Obstet Gynecol. 2021;224(2).

107. Lamminpaa R, Vehvilainen-Julkunen K, Gissler M, Heinonen S. Preeclampsia complicated by advanced maternal age: a registry-based study on primiparous women in Finland 1997-2008. BMC Pregnancy Childb. 2012;12.

108. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005;365(9461):785-99.

109. Witlin AG, Saade GR, Mattar F, Sibai BM. Risk factors for abruptio placentas and eclampsia: Analysis of 445 consecutively managed women with severe preeclampsia and eclampsia. Am J Obstet Gynecol. 1999;180(6):1322-6.

110. Kametas N ND, Nicolaides K. Chronic hypertension and superimposed preeclampsia: Screening and diagnosis. Am J Obstet Gynecol. 2021(In Press).

111. McCowan LME, Buist RG, North RA, Gamble G. Perinatal morbidity in chronic hypertension. BJOG. 1996;103(2):123-9.

112. Sibai BM. Diagnosis and management of gestational hypertension and Preeclampsia. Obstetrics and Gynecology. 2003;102(1):181-92.

113. Negrato CA, Jovanovic L, Tambascia MA, Geloneze B, Dias A, Calderon IDP, et al. Association between insulin resistance, glucose intolerance, and hypertension in pregnancy. Metab Syndr Relat Disord. 2009;7(1):53-9.

114. Salomon C, Rice GE. Role of Exosomes in Placental Homeostasis and Pregnancy Disorders. Prog Mol Biol Transl. 2017;145:163-79.

115. Han C, Han LL, Huang PZ, Chen YY, Wang YM, Xue FX. Syncytiotrophoblast-derived extracellular vesicles in pathophysiology of preeclampsia. Front Physiol. 2019;10.

116. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. New Engl J Med. 2006;355(10):992-1005.

117. Stepan H, Herraiz I, Schlembach D, Verlohren S, Brennecke S, Chantraine F, et al. Implementation of the sFlt-1/PIGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: Implications for clinical practice. Ultrasound Obst Gyn. 2015;45(3):241-6.

118. Murthi P, Brennecke SP. The placenta is the villain or victim in the pathogenesis of pre-eclampsia. BJOG. 2021;128(2):147-148.

119. Thilaganathan B. The placenta is the villain or victim in the pathogenesis of pre-eclampsia. BJOG.2020;128(BJOG perspectives):148.

120. Melchiorre K, Giorgione V, Thilaganathan B. The placenta and preeclampsia: villain or victim? Am J Obstet Gynecol. 2021. https://doi.org/10.1016/j.ajog.2020.10.024.

121. Lisonkova S, Razaz N, Sabr Y, Muraca GM, Boutin A, Mayer C, et al. Maternal risk factors and adverse birth outcomes associated with HELLP syndrome: a population-based study. BJOG. 2020;127(10):1189-98.

122. Fishel Bartal M, Sibai BM. Eclampsia in the 21st century. Am J Obstet Gynecol. 2020 Sep 24:S0002-9378(20)31128-5. doi: 10.1016/j.ajog.2020.09.037. Epub ahead of print.

123. Pollock W, Peek MJ, Wang A, Li Z, Ellwood D, Homer CSE, et al. Eclampsia in Australia and New Zealand: A prospective population-based study. Aust N Z J Obstet Gynaecol. 2020;60(4):533-40.

124. Gabbe SG, Graves CR. Management of diabetes mellitus complicating pregnancy. Obstetrics and Gynecology. 2003;102(4):857-68.

125. Dowswell T, Middleton P, Weeks A. Antenatal day care units versus hospital admission for women with complicated pregnancy. Cochrane Database Syst Rev. 2009(4):CD001803.

126. Dunlop L, Umstad M, McGrath G, Reidy K, Brennecke S. Cost-effectiveness and patient satisfaction with pregnancy day care for hypertensive disorders of pregnancy. Aust N Z J Obstet Gynaecol. 2003;43(3):207-12.

127. de Haas S, Ghossein-Doha C, van Kuijk SM, van Drongelen J, Spaanderman ME. Physiological adaptation of maternal plasma volume during pregnancy: A systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017;49(2):177-87.

128. Margulies M, Zin C, Margulies ND, Voto LS. Noninvasive Ambulatory Blood-Pressure Control in Normotensive Pregnant-Women. Am J Hypertens. 1989;2(12):924-6.

129. Tucker KL, Hodgkinson J, Wilson HM, Crawford C, Stevens R, Lay-Flurrie S, et al. Current prevalence of self-monitoring of blood pressure during pregnancy: the BUMP Survey. J Hypertens. 2021;39(5):994-1001.

130. Pealing LM, Tucker KL, Mackillop LH, Crawford C, Wilson H, Nickless A, et al. A randomised controlled trial of blood pressure self-monitoring in the management of hypertensive pregnancy. OPTIMUM-BP: A feasibility trial. Pregnancy Hypertens. 2019;18:141-9.

131. Steer PJ, Little MP, Kold-Jensen T, Chapple J, Elliott P. Maternal blood pressure in pregnancy, birth weight, and perinatal mortality in first births: Prospective study. Brit Med J. 2004;329(7478):1312-18.

132. Scott G, Gillon TE, Pels A, von Dadelszen P, Magee LA. Guidelines-similarities and dissimilarities: A systematic review of international clinical practice guidelines for pregnancy hypertension. Am J Obstet Gynecol. 2020 Aug 20:S0002-9378(20)30846-2. doi: 10.1016/j.ajog.2020.08.018. Epub ahead of print..

133. Sridharan K, Sequeira RP. Drugs for treating severe hypertension in pregnancy: A network meta-analysis and trial sequential analysis of randomized clinical trials. Br J Clin Pharmacol. 2018;84(9):1906-16.

134. Magee LA, Abalos E, von Dadelszen P, Sibai B, Walkinshaw SA. Control of hypertension in pregnancy. Curr Hypertens Rep. 2009;11(6):429-36.

135. Sibai BM. The benefits/risks of treatment of non-severe hypertension in pregnancy and choice of drug remain unanswered. BJOG. 2016;123(7):1142.

136. Clinical Trials Registry USA- CHAP trial [Internet] [cited 2021 May 8] Available from: https://clinicaltrials.gov/ct2/show/study/NCT02299414.

137. El Guindy AA, Nabhan AF. A randomized trial of tight vs. less tight control of mild essential and gestational hypertension in pregnancy. J Perinat Med. 2008;36(5):413-8.

138. Magee LA, von Dadelszen P, Chan S, Gafni A, Gruslin A, Helewa M, et al. The Control of Hypertension In Pregnancy Study pilot trial. BJOG. 2007;114(6):770, e13-20.

139. Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Db Syst Rev. 2001(2):CD002252.

140. Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Db Syst Rev. 2007(1).

141. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Db Syst Rev. 2014(2).

142. Australian Medicines Handbook 2021 [Internet]. Adelaide: Australian Medicines Handbook Pty Ltd; 2021 January.[cited 2021 Jun 14].Available from: https://amhonline.amh.net.au/

143. Battarbee AN, Sinkey RG, Harper LM, Oparil S, Tita ATN. Chronic hypertension in pregnancy. Am J Obstet Gynecol. 2020;222(6):532-41.

144. Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Db Syst Rev. 2019;2019(10).

145. Roberge S, Nicolaides KH, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: A meta-analysis. Ultrasound Obstet Gynecol. 2013;41(5):491-9.

146. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med. 2017;377(7):613-22.

147. Hofmeyr GJ, Lawrie TA, Atallah AN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Db Syst Rev. 2018;10:CD001059.

148. Groom KM, McCowan LM, Mackay LK, Lee AC, Said JM, Kane SC, et al. Enoxaparin for the prevention of preeclampsia and intrauterine growth restriction in women with a history: A randomized trial. Am J Obstet Gynecol. 2017;216(3):296 e1- e14.

149. Rodger MA, Gris JC, de Vries JIP, Martinelli I, Rey E, Schleussner E, et al. Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: A meta-analysis of individual patient data from randomised controlled trials. Lancet. 2016;388(10060):2629-41.

150. Cruz-Lemini M, Vazquez JC, Ullmo J , Llurba E, . Low-molecular-weight heparin for prevention of preeclampsia and other placenta-mediated complications: A systematic review and meta-analysis. Am J Obstet Gynecol. 2021.(In press) doi:https://doi.org/10.1016/j.ajog.2020.11.006

151. Brownfoot FC, Hastie R, Hannan NJ, Cannon P, Tuohey L, Parry LJ, et al. Metformin as a prevention and treatment for preeclampsia: effects on soluble fms-like tyrosine kinase 1 and soluble endoglin secretion and endothelial dysfunction. Am J Obstet Gynecol. 2016;214(3):356 e1- e15.

152. de Alwis N, Beard S, Mangwiro YT, Binder NK, Kaitu'u-Lino TJ, Brownfoot FC, et al. Pravastatin as the statin of choice for reducing pre-eclampsia-associated endothelial dysfunction. Pregnancy Hypertens. 2020;20:83-91.

153. Binder NK, Brownfoot FC, Beard S, Cannon P, Nguyen TV, Tong S, et al. Esomeprazole and sulfasalazine in combination additively reduce sFlt-1 secretion and diminish endothelial dysfunction: potential for a combination treatment for preeclampsia. Pregnancy Hypertens. 2020;22:86-92.

154. Tong S, Kaitu'u-Lino TJ, Hastie R, Brownfoot F, Cluver C, Hannan N. Pravastatin, proton-pump inhibitors, metformin, micronutrients, and biologics: new horizons for the prevention or treatment of preeclampsia. Am J Obstet Gynecol. 2020 Sep 16:S0002-9378(20)31071-1. doi: 10.1016/j.ajog.2020.09.014. Epub ahead of print.

155. Mongelli M, Figueras F, Francis A, Gardosi J. A customized birthweight centile calculator developed for an Australian population. Aust N Z J Obstet Gynaecol. 2007;47(2):128-31.

156. Ahmad AS, Samuelsen SO. Hypertensive disorders in pregnancy and fetal death at different gestational lengths: A population study of 212,1371 pregnancies. BJOG. 2012;119(12):1521-8.

157. Ram M, Berger H, Geary M, McDonald SD, Murray-Davis B, Riddell C, et al. Timing of delivery in women with chronic hypertension. Obstet Gynecol. 2018;132(3):669-77.

158. Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): A multicentre, open-label randomised controlled trial. Lancet. 2009;374(9694):979-88.

159. Langenveld J, Broekhuijsen K, van Baaren GJ, van Pampus MG, van Kaam AH, Groen H, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia between 34 and 37 weeks' gestation (HYPITAT-II): A multicentre, open-label randomised controlled trial. BMC Preg Childbirth. 2011;11:50.

160. Hauth JC, Ewell MG, Levine RJ, Esterlitz JR, Sibai B, Curet LB, et al. Pregnancy outcomes in healthy nulliparas who developed hypertension. Obstetrics and Gynecology. 2000;95(1):24-8.

161. Li F, Wang T, Chen L, Zhang S, Chen L, Qin J. Adverse pregnancy outcomes among mothers with hypertensive disorders in pregnancy: A meta-analysis of cohort studies. Pregnancy Hypertens. 2021;24:107-17.

162. Mayo Clinic. Preterm birth [Internet]. [cited 2021 May 5].Available from: https://www.mayoclinic.org/diseases-conditions/premature-birth/symptoms-causes/syc-20376730.

163. Abdel Razeq NM, Khader YS, Batieha AM. The incidence, risk factors, and mortality of preterm neonates: A prospective study from Jordan (2012-2013). Turk J Obstet Gynecol. 2017;14(1):28-36.

164. Lu CQ, Lin J, Yuan L, Zhou JG, Liang K, Zhong QH, et al. Pregnancy induced hypertension and outcomes in early and moderate preterm infants. Pregnancy Hypertens. 2018;14:68-71.

165. Kumarathasan P, Williams G, Bielecki A, Blais E, Hemmings DG, Smith G, et al. Characterization of maternal plasma biomarkers associated with delivery of small and large for gestational age infants in the MIREC study cohort. PLoS One. 2018;13(11):e0204863.

166. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: Systematic review and meta-analysis.Brit Med J. 2014;348.

167. Mulualem G, Wondim A, Woretaw A. The effect of pregnancy induced hypertension and multiple pregnancies on preterm birth in Ethiopia: A systematic review and meta-analysis. BMC Res Notes. 2019;12(1):91.

168. Magee LA, Yong PJ, Espinosa V, Cote AM, Chen I, von Dadelszen P. Expectant management of severe preeclampsia remote from term: a structured systematic review. Pregnancy Hypertens. 2009;28(3):312-47.

169. Hall DR, Odendaal HJ, Steyn DW, Grove D. Expectant management of early onset, severe pre-eclampsia: Maternal outcome. BJOG. 2000;107(10):1252-7.

170. Hall DR, Odendaal HJ, Steyn DW. Expectant management of severe pre-eclampsia in the mid-trimester. Eur J Obstet Gynecol Reprod Biol. 2001;96(2):168-72.

171. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet. 2002;359(9321):1877-90.

172. Sibai BM. Chronic hypertension in pregnancy. Obstet Gynecol. 2002;100(2):369-77.

173. Ankumah NE, Sibai BM. Chronic hypertension in pregnancy: Diagnosis, management, and outcomes. Clin Obstet Gynecol. 2017;60(1):206-14.

174. Panaitescu AM, Syngelaki A, Prodan N, Akolekar R, Nicolaides KH. Chronic hypertension and adverse pregnancy outcome: A cohort study. Ultrasound Obstet Gynecol. 2017;50(2):228-35.

175. Mooney SS, Lee RM, Tong S, Brownfoot FC. Expectant management of severe preterm preeclampsia: a comparison of maternal and fetal indications for delivery. J Matern Fetal Neonatal Med. 2016;29(23):3821-6.

176. von Dadelszen P, Payne B, Li J, Ansermino JM, Broughton Pipkin F, Cote AM, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Lancet. 2011;377(9761):219-27.

177. Thangaratinam S, Allotey J, Marlin N, Dodds J, Cheong-See F, von Dadelszen P, et al. Prediction of complications in early-onset pre-eclampsia (PREP): development and external multinational validation of prognostic models. BMC Med. 2017;15(1):68.

178. Brown MA, Roberts L, Hoffman A, Henry A, Mangos G, O'Sullivan A, et al. Recognizing Cardiovascular Risk After Preeclampsia: The P4 Study. J Am Heart Assoc. 2020;9(22).

179. Stuart JJ, Tanz LJ, Missmer SA, Rimm EB, Spiegelman D, James-Todd TM, et al. Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development: An observational cohort study. Ann Intern Med. 2018;169(4):224-32.

180. Benschop L, Duvekot JJ, Roeters van Lennep JE. Future risk of cardiovascular disease risk factors and events in women after a hypertensive disorder of pregnancy. Heart. 2019;105(16):1273-8.

181. Heida KY, Franx A, van Rijn BB, Eijkemans MJ, Boer JM, Verschuren MW, et al. Earlier age of onset of chronic hypertension and type 2 diabetes mellitus after a hypertensive disorder of pregnancy or gestational diabetes mellitus. Hypertension. 2015;66(6):1116-22.

182 Giorgione V, Ridder A, Kalafat E, Khalil A, Thilaganathan B. Incidence of postpartum hypertension within 2 years of a pregnancy complicated by pre-eclampsia: A systematic review and meta-analysis. BJOG. 2021;128(3):495-503.

183. Theilen LH, Meeks H, Fraser A, Esplin MS, Smith KR, Varner MW. Long-term mortality risk and life expectancy following recurrent hypertensive disease of pregnancy. Am J Obstet Gynecol. 2018;219(1):107 e1-e6.

184. Arnott C, Nelson M, Ramirez MA, Hyett J, Gale M, Henry A, et al. Maternal cardiovascular risk after hypertensive disorder of pregnancy. Heart. 2020;106(24):1927-33.

185. Leon LJ, McCarthy FP, Direk K, Gonzalez-Izquierdo A, Prieto-Merino D, Casas JP, et al. Preeclampsia and Cardiovascular Disease in a Large UK Pregnancy Cohort of Linked Electronic Health Records: A CALIBER Study. Circulation. 2019;140(13):1050-60.

186. Behrens I, Basit S, Lykke JA, Ranthe MF, Wohlfahrt J, Bundgaard H, et al. Association Between Hypertensive Disorders of Pregnancy and Later Risk of Cardiomyopathy. JAMA. 2016;315(10):1026-33.

187. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. Br Med J. 2007;335(7627):974.

188. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J. 2008;156(5):918-30.

189. Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, et al. Preeclampsia and future cardiovascular health: A systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2017;10(2).

190. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): Population-based retrospective cohort study. Lancet. 2005;366(9499):1797-803.

191. Engeland A, Bjorge T, Daltveit AK, Skurtveit S, Vangen S, Vollset SE, et al. Risk of diabetes after gestational diabetes and preeclampsia. A registry-based study of 230,000 women in Norway. Eur J Epidemiol. 2011;26(2):157-63.

192. Khashan AS, Evans M, Kublickas M, McCarthy FP, Kenny LC, Stenvinkel P, et al. Preeclampsia and risk of end stage kidney disease: A Swedish nationwide cohort study. PLoS Med. 2019;16(7):e1002875.

193. Kristensen JH, Basit S, Wohlfahrt J, Damholt MB, Boyd HA. Pre-eclampsia and risk of later kidney disease: Nationwide cohort study. Br Med J. 2019;365:l1516.

194. Elharram M, Dayan N, Kaur A, Landry T, Pilote L. Long-term cognitive impairment after preeclampsia: A systematic review and meta-analysis. Obstet Gynecol. 2018;132(2):355-64.

195. Zwertbroek EF, Franssen MTM, Broekhuijsen K, Langenveld J, Bremer H, Ganzevoort W, et al. Neonatal developmental and behavioral outcomes of immediate delivery versus expectant monitoring in mild hypertensive disorders of pregnancy: 2-year outcomes of the HYPITAT-II trial. Am J Obstet Gynecol. 2019;221(2):154 e1-e11.

196. Maher GM, O'Keeffe GW, Kearney PM, Kenny LC, Dinan TG, Mattsson M, et al. Association of hypertensive disorders of pregnancy with risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis. JAMA Psychiatry. 2018;75(8):809-19.

197. Kanata M, Liazou E, Chainoglou A, Kotsis V, Stabouli S. Clinical outcomes of hypertensive disorders in pregnancy in the offspring during perinatal period, childhood, and adolescence. J Hum Hypertens. 2021. https://doi.org/10.1038/s41371-021-00550-3

198. Scaffidi J, Mol BW, Keelan JA. The pregnant women as a drug orphan: a global survey of registered clinical trials of pharmacological interventions in pregnancy. BJOG. 2017;124(1):132-40.

199. Butters L, Kennedy S, Rubin PC. Atenolol in Essential-Hypertension during Pregnancy. Br Med J. 1990;301(6752):587-9.

200. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. Cochrane Db Syst Rev. 2003(3):CD002863.

201. von Dadelszen P, Ornstein M.P, Bull S.B, Logan A.G, Koren G, Magee L.A. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. Lancet. 2000;355:87-92.

202. Waterman EJ, Magee LA, Lim KI, Skoll A, Rurak D, von Dadelszen P. Do commonly used oral antihypertensives alter fetal or neonatal heart rate characteristics? A systematic review. Pregnancy Hypertens. 2004;23(2):155-69.

203. Magee LA, von Dadelszen P. State-of-the-Art Diagnosis and Treatment of Hypertension in Pregnancy. Mayo Clin Proc. 2018;93(11):1664-77.

204. Magee LA, Namouz-Haddad S, Cao V, Koren G, von Dadelszen P. Labetalol for hypertension in pregnancy. Expert Opin Drug Saf. 2015;14(3):453-61.

205. Yakoob MY, Bateman BT, Ho E, Hernandez-Diaz S, Franklin JM, Goodman JE, et al. The risk of congenital malformations associated with exposure to beta-blockers early in pregnancy: A meta-analysis. Hypertension. 2013;62(2):375-81.

206. Wu Y, Yao JW, Xu LJ, Chen M, Wan L. Risk of congenital malformations in offspring of women using beta-blockers during early pregnancy: An updated meta-analysis of observational studies. Brit J Clin Pharmaco. 2021;87(3):806-15.

207. Steiner J.F EMA. Lingua Medica: The language of medication-taking. Ann Inter Med. 2000;132(11):926-30.

208. Bennett, D. (1980). Compliance in Health Care. Edited by R. Brian Haynes, D. Wayne Taylor and David L. Sackett, London: The Johns Hopkins University Press. 1979. p 516. British Journal of Psychiatry, 137(2), 190-190. doi:10.1192/S0007125000105082

209. Oxford University Press. Oxford English Dictionary.2020 [Internet] UK. [cited 2020 Mar 11]. Available at www.oed.com

210. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: Three decades of research. A comprehensive review. J Clin Pharm Ther. 2001;26(5):331-42.

211. Meichenbaum, D., & Turk, D.C. (1987). Facilitating treatment adherence: A practitioner's guidebook. Plenum Press

212. Nafradi L, Galimberti E, Nakamoto K, Schulz PJ. Intentional and unintentional medication non-adherence in hypertension: the role of health literacy, empowerment and medication beliefs. J Public Health Res. 2016;5(3):111-5.

213. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691-705.

214. Sackett DL, Gibson ES, Taylor DW, Haynes RB, Hackett BC, Roberts RS, et al. Randomized clinical trial of strategies for improving medication compliance in primary hypertension. Lancet. 1975;1(7918):1205-7.

215. Burnier M, Egan BM. Adherence in hypertension: A review of prevalence, risk factors, impact, and management. Circulation Research. 2019;124(7):1124-40.

216. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. Br Med J. 2008;336(7653):1114-7.

217. Braunthal S, Brateanu A. Hypertension in pregnancy: Pathophysiology and treatment. Sage Open Med. 2019;7.

218. Olesen C, Sondergaard C, Thrane N, Nielsen GL, de Jong-van den Berg L, Olsen J. Do pregnant women report use of dispensed medications? Epidemiology. 2001;12(5):497-501.

219. Lupattelli A, Spigset O, Nordeng H. Adherence to medication for chronic disorders during pregnancy: Results from a multinational study. Int J Clin Pharm-Net. 2014;36(1):145-53.

220. Sanz E, Gomez-Lopez T, Martinez-Quintas MJ. Perception of teratogenic risk of common medicines. Eur J Obstet Gyn R B. 2001;95(1):127-31.

221. Widnes SF, Schjott J. Risk perception regarding drug use in pregnancy. Am J Obstet Gynecol. 2017;216(4):375-8.

222. Hancock RL, Koren G, Einarson A, Ungar WJ. The effectiveness of teratology information services (TIS). Reproductive Toxicology. 2007;23(2):125-32.

223. Mulder B, Bijlsma MJ, Schuiling-Veninga CCM, Morssink LP, van Puijenbroek E, Aarnoudse JG, et al. Risks versus benefits of medication use during pregnancy: What do women perceive? Patient Prefer Adher. 2018;12:1-8.

224. Rizk MA, Abdel-Aziz F, Ashmawy AA, Mahmoud AA, Abuzeid TM. Knowledge and practices of pregnant women in relation to the intake of drugs during pregnancy. J Egypt Public Health Assoc. 1993;68(5-6):567-91.

225. Nordeng H, Koren G, Einarson A. Pregnant women's beliefs about medications: A study among 866 Norwegian women. Ann Pharmacother. 2010;44(9):1478-84.

226. Munoz SR, Lupattelli A, de Vries ST, Mol PGM, Nordeng H. Differences in medication beliefs between pregnant women using medication, or not, for chronic diseases: a cross-sectional, multinational, web-based study. BMJ Open. 2020;10(2).

227. McDonald K, Amir LH, Davey MA. Maternal bodies and medicines: A commentary on risk and decision-making of pregnant and breastfeeding women and health professionals. BMC Public Health. 2011;11.

228. Widnes SF, Schjott J, Granas AG. Risk perception and medicines information needs in pregnant women with epilepsy - A qualitative study. Seizure-Eur J Epilep. 2012;21(8):597-602.

229. Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR. Prevalence of depression during pregnancy: Systematic review. Obstet Gynecol. 2004;103(4):698-709.

230. Biaggi A, Conroy S, Pawlby S, Pariante CM. Identifying the women at risk of antenatal anxiety and depression: A systematic review. J Affect Disord. 2016;191:62-77.

231. Kurki T, Hiilesmaa V, Raitasalo R, Mattila H, Ylikorkala O. Depression and anxiety in early pregnancy and risk for preeclampsia. Obstet Gynecol. 2000;95(4):487-90.

232. Zuckerman B AH, Bauchner H, Cabral H. Depressive symptoms during pregnancy: Relationship to poor health behaviors. Am J of Obstet and Gynaecol. 1989;160(5):1107-11.

233. Kothari A, de Laat J, Dulhunty JM, Bruxner G. Perceptions of pregnant women regarding antidepressant and anxiolytic medication use during pregnancy. Australas Psychiatry. 2019;27(2):117-20.

234. Hameen-Anttila K, Nordeng H, Kokki E, Jyrkka J, Lupattelli A, Vainio K, et al. Multiple information sources and consequences of conflicting information about medicine use during pregnancy: A multinational Internet-based survey. J Med Internet Res. 2014;16(2):e60.

235. Denton LK, Creeley CE, Stavola B, Hall K, Foltz BD. An analysis of online pregnancy message boards: Mother-to-mother advice on medication use. Women Birth. 2020;33(1):e48-e58.

236. Henry A, Crowther C. Sources of advice on medication use in pregnancy and reasons for medication uptake and cessation during pregnancy. Aust N Z J Obstet Gynaecol. 2000;40(2):173-5.

237. Victoria. Health Department. & Ministerial Review into Birthing Service in Victoria. 1990, Having a baby in Victoria : final report of the Ministerial Review of Birthing Services in Victoria. Health Dept. Victoria Melbourne.

238. Tastekin Ouyaba A, Infal Kesim S. The effect of the Internet on decision-making during pregnancy: A systematic review. Arch Womens Ment Health. 2021;24(2):205-15.

239. Rouhi M, Stirling C, Crisp EP. The 'fallacy of normalcy': A content analysis of women's online post-childbirth health-related support. Women Birth. 2021;34(3):e262-e70.

240. Pijpers EL, Kreijkamp-Kaspers S, McGuire TM, Deckx L, Brodribb W, van Driel ML. Women's questions about medicines in pregnancy: An analysis of calls to an Australian national medicines call centre. Aust N Z J Obstet Gynaecol. 2017;57(3):334-41.

241. van Trigt AM, Waardenburg CM, Haaijer-Ruskamp FM, de Jong-van den Berg LT. Questions about drugs: How do pregnant women solve them? Pharm World Sci. 1994;16(6):254-9.

242. NPS MedicineWise. Hydopa: Consumer Medicines Information [Internet]. [cited 2021 June 16]. Available from: https://www.nps.org.au/medicine-finder/hydopa-tablets.

243. Ceulemans M, Lupattelli A, Nordeng H, Odalovic M, Twigg M, Foulon V. Women's beliefs about medicines and adherence to pharmacotherapy in pregnancy: Opportunities for community pharmacists. Curr Pharm Des. 2019;25(5):469-82.

244. Shanmugalingam R, Mengesha Z, Notaras S, Liamputtong P, Fulcher I, Lee G, et al. Factors that influence adherence to aspirin therapy in the prevention of preeclampsia amongst high-risk pregnant women: A mixed method analysis. PloS One. 2020;15(2).

245. Shanmugalingam R, Wang XS, Motum P, Fulcher I, Lee G, Kumar R, et al. Clinical influence of nonadherence with prophylactic aspirin in preventing preeclampsia in high-risk pregnancies: A multicenter, prospective, observational cohort study. Hypertension. 2020;75(4):1125-32.

246. Atallah A, Lecarpentier E, Goffinet F, Doret-Dion M, Gaucherand P, Tsatsaris V. Aspirin for Prevention of Preeclampsia. Drugs. 2017;77(17):1819-31.

247. Ortved D, Hawkins TLA, Johnson JA, Hyett J, Metcalfe A. Cost-effectiveness of first-trimester screening with early preventative use of aspirin in women at high risk of early-onset pre-eclampsia. Ultrasound Obst Gyn. 2019;53(2):239-44.

248. Wertaschnigg D, Reddy M, Mol BWJ, Rolnik DL, Costa FD. Prenatal screening for pre-eclampsia: Frequently asked questions. Aust N Z J Obstet Gyn. 2019;59(4):477-83.

249. Broekhuijsen K, van Baaren GJ, van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy

between 34 and 37 weeks of gestation (HYPITAT-II): An open-label, randomised controlled trial. Lancet. 2015;385(9986):2492-501.

250. Barlow JH, Hainsworth J, Thornton S. Women's experiences of hospitalisation with hypertension during pregnancy: Feeling a fraud. J Reprod Infant Psyc. 2008;26(3):157-67.

251. Roberts LM, Davis GK, Homer CS. Pregnancy with gestational hypertension or preeclampsia: A qualitative exploration of women's experiences. Midwifery. 2017;46:17-23.

252. Davis, G.K., Henry, A., Arnott, C. and Brown, M.A. (2021), The long-term cardiovascular impact of hypertension in pregnancy – A missed opportunity. Aust N Z J Obstet Gynaecol, 61: 474-477. https://doi.org/10.1111/ajo.13335

253. Parikh NI, Gonzalez JM, Anderson CAM, Judd SE, Rexrode KM, Hlatky MA, et al. Adverse Pregnancy Outcomes and Cardiovascular Disease Risk: Unique Opportunities for Cardiovascular Disease Prevention in Women: A Scientific Statement From the American Heart Association. Circulation. 2021;143(18):E902-E16.

254. Aslam A, Perera S, Watts M, Kaye D, Layland J, Nicholls SJ, et al. Previous Pre-Eclampsia, Gestational Diabetes and Hypertension Place Women at High Cardiovascular Risk But Do We Ask? Heart Lung Circ. 2021;30(1):154-7.