AMBULATORY BLOOD PRESSURE MONITORING IN HYPERTENSIVE PREGNANCIES

By

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ABSTRACT

This thesis focuses on outcomes in hypertension in pregnancy, and the role of ambulatory blood pressure monitoring (ABPM). Overviews of blood pressure measurement and hypertension in pregnancy are followed by discussion of ABPM in non-pregnant and pregnant individuals. A literature review of research in ABPM in pregnancy is presented, revealing good prediction of certain outcomes. ABPM is recommended in chronic hypertension, identifying white coat hypertension and targeting intervention appropriately in pregnancy. An extensive database of hypertensive pregnancies is then analysed to assess outcomes in a local multi-ethnic population. Women with chronic hypertension are examined separately. Very high rates of stillbirth are evident, especially in women of Asian and Black ethnicity with growth-restricted babies.

ABPM is then compared with sphygmomanometer measurements in 100 women using regression analysis, assessing prediction of perinatal outcomes. ABPM is superior in predicting low birth weight, prematurity and proteinuria. Finally, the first randomized controlled trial (RCT) of ABPM in pregnancy is presented. Hypertensive pregnant women were randomized to revealed or concealed ABPM results. Fewer women in the 'revealed' group underwent induction of labour for hypertension. However, the reduction in overall rates of induction did not reach significance. Patient satisfaction was high. Randomized trials of ABPM in pregnancy are viable. Further RCTs particularly in chronic hypertensives are recommended.

DEDICATION

I dedicate this thesis to my family, with thanks and love:

To my husband Matthew for his patience and support over the years,

and my children Sam and Ellen.

ACKNOWLEDGEMENTS

This work was undertaken while I was a clinical research fellow at Good Hope Hospital from April 2002 to February 2004.

I would like to acknowledge and thank:

-Mr David Churchill, my supervisor, for formulating the protocols for the two ambulatory blood pressure monitoring studies, providing ongoing support and advice, and obtaining funding for the first year of research.

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-All the women who agreed to participate in the trial

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LIST OF ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
ANOVA	Analysis of variance
CBP(M)	Conventional blood pressure (monitoring)
CDBP	Conventional diastolic blood pressure
CH	Chronic hypertension
CI	Confidence intervals
CS	Caesarean section
CSBP	Conventional systolic blood pressure
DBP	Diastolic blood pressure
GH	Gestation hypertension
HELLP	Haemolysis elevated liver enzymes low platelets
IOL	Induction of labour
ISSHP	International Society for the Study of Hypertension in Pregnancy
IQR	Interquartile range
IUGR	Intrauterine growth restriction
mmHg	Millimetres of mercury
NK	Not known
PE	Pre-eclampsia
PIH	Pregnancy induced hypertension
PPV	Positive predictive value
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SD	Standard deviation

SH	Secondary hypertension
SPE	Superimposed pre-eclampsia
TRH	Thyrotophin releasing hormone
WCH	White coat hypertension

PRESENTATIONS AND PUBLICATIONS

FROM THIS THESIS

British Maternal and Fetal Medicine Society, Annual Conference, York University, 2003:

Poster presentation: 'A comparison of ambulatory and conventional blood pressure monitoring as predictors of obstetric and neonatal outcomes'. **CA Rhodes**, D Churchill, T Marshall.

Rhodes CA, Churchill D, Marshall T. A comparison of ambulatory conventional blood pressure monitoring as predictors of obstetric and neonatal outcomes. J Obstet Gynaecol 2003;23 (suppl 1):S73.

International Society for Study of Hypertension in Pregnancy: British Meeting, Glasgow 2003:

Oral presentation: 'Obstetric and neonatal outcomes in 645 women attending an antenatal hypertension clinic.' **CA Rhodes**, D Churchill, DG Beevers.

Birmingham and Midland Obstetrics and Gynaecology Society, Prague Meeting, 2004:

Oral presentation: 'Obstetric and neonatal outcomes in 645 women attending an antenatal hypertension clinic.' **CA Rhodes**, D Churchill, DG Beevers.

British Maternal and Fetal Medicine Society, Annual Conference, Nottingham University, 2005:

Oral presentation: 'A randomized comparison of ambulatory blood pressure measurement versus conventional blood pressure measurement for the management of pregnant hypertensive women.' **CA Rhodes,** D Churchill.

Rhodes C, Churchill D. ‘A randomized comparison of ambulatory blood pressure measurement (ABPM), versus conventional blood pressure measurement, for the management of pregnant hypertensive women.’ J Obstet Gynaecol 2005;25 (suppl 1):S16.

CHAPTER 1:

INTRODUCTION

1.1 INTRODUCTION

1.1.1 General Introduction

Blood pressure measurement is embedded in the care of pregnant women. It is a standard test used globally to screen for hypertension. The burden of morbidity and mortality related to increased blood pressure in pregnancy for both mothers and babies is well-documented. More recent research has suggested long-term health implications for babies born to women with hypertension. Raised blood pressure in pregnancy may reflect failure of maternal cardiovascular adaptations to the pregnant state, resulting in an undernourished fetus of low birth weight at subsequent risk of coronary heart disease, stroke and hypertension.[1] The longer term implications for mothers are also becoming evident: women with pre-eclampsia have a raised long term risk of cardiovascular disease, occurring at an earlier age.[2]

Much effort has been directed to improving the detection, prevention and management strategies for this common pregnancy complication. In spite of this, controversies remain concerning defining the problem, technical aspects of measuring blood pressure, the nature of the underlying patho-physiology, and how best to manage the various presentations of hypertension in pregnancy.

This thesis has five chapters, all related to issues in hypertension in pregnancy. A background section will discuss the history of blood pressure measurement, hypertension in pregnancy and the use of ambulatory blood pressure monitoring (ABPM) generally and in pregnancy. The second chapter concerns outcomes in women with raised blood pressure. Prospectively recorded details of women from a multi-ethnic population, attending a

specialist antenatal hypertension clinic over a 22-year period, will be reviewed with particular reference to obstetric and neonatal outcomes. In the third chapter, the notes of 100 pregnant women will be reviewed to assess the predictive value of ABPM for obstetric and neonatal outcomes in comparison with conventional blood pressure monitoring. Following this, the results of a prospective randomized trial of the use of ABPM in pregnancy will be presented in the fourth chapter. Finally, the fifth chapter summarises the conclusions and recommendations.

1.1.2 Literature search

An initial Medline search was performed for background information and to write the research protocol, using search terms 'Hypertension' 'Pregnancy' 'Ambulatory blood pressure monitoring' 'ABPM' 'chronic hypertension' and 'pre-eclampsia', with appropriate alternate spellings and truncated terms. Full text articles were then obtained from the Good Hope Hospital Library, British Medical Association, Royal College of Obstetricians and Gynaecologists (RCOG) libraries or via the National Electronic Library for Health (NELH)/RCOG where available electronically.

Following this, a formal systematic search was conducted with the aid of a clinical librarian, with the aim of identifying publications in two fields. The first search was for reviews, meta-analyses and clinical trials relating to hypertension in pregnancy, to identify recent advances and important studies. This was to provide background information for the thesis. The second search related to any type of publication on the use of ABPM in pregnancy, to access all publications relevant to this thesis. The exact search terms are listed in Appendix 1.

In the general ‘hypertension in pregnancy’ search, 974 citations were identified. Citations were reviewed by the research fellow with advice from the clinical librarian. The abstracts of every identified publication were read if available. If the abstract was not published, the full papers were obtained. Publications which focused on classification of hypertension in pregnancy, pregnancy outcomes, and updates on pathophysiology and management were ordered in full text from the libraries above.

In the ‘ABPM in pregnancy’ search, 106 citations were found. All abstracts were reviewed; if the abstract was unavailable the full text article was requested. Relevance was agreed with the research supervisor, and the full text article obtained for all publications deemed as relevant. If there was uncertainty on relevance on reading the abstract, the full text article was obtained for review. Reference lists of all articles retrieved were hand searched to check for further papers.

Articles on automated or self-initiated blood pressure measurement which were not strictly related to ABPM were excluded. At the end of the search process, all 91 relevant papers were classified by subject or publication type, and are reviewed in sections 1.4.2 and 1.4.3. No randomized controlled trials were found.

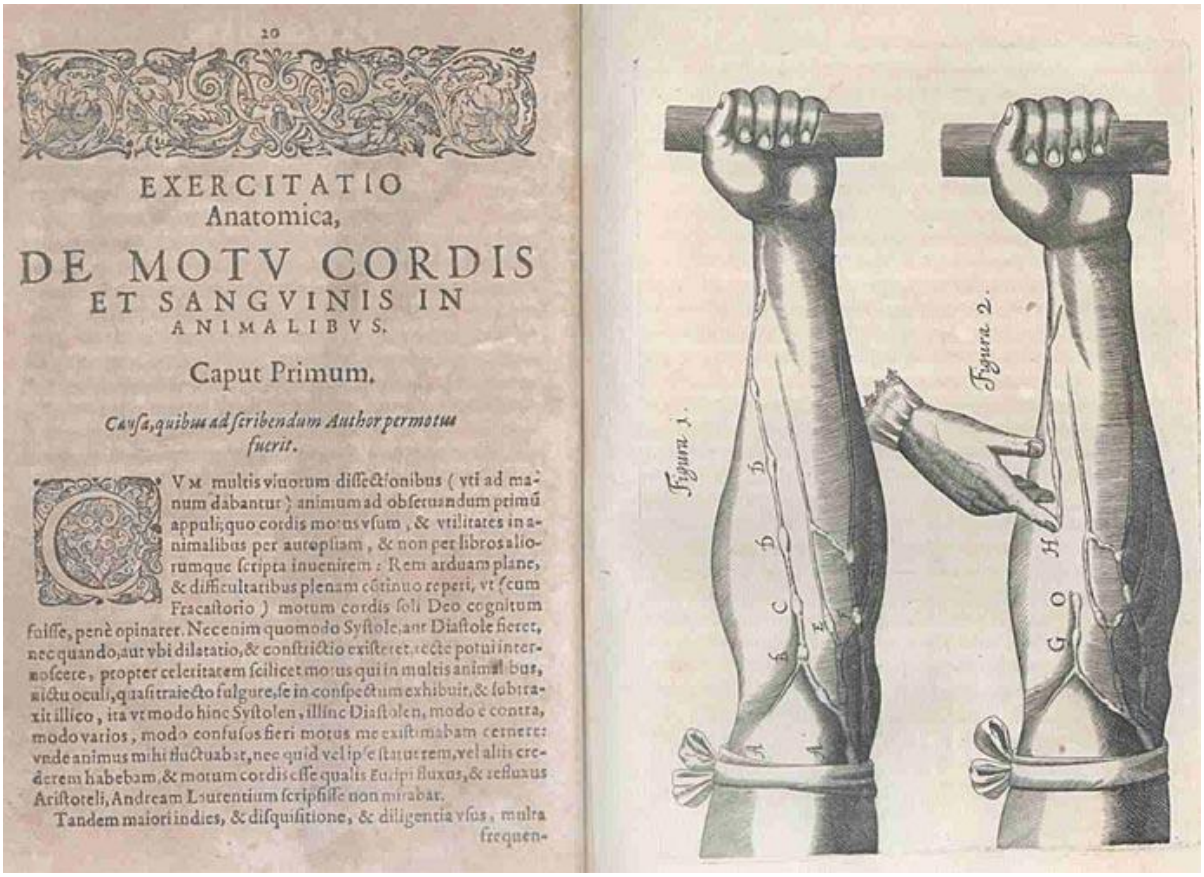
All publications relating to the database reported in Chapter Two were available from the previous research fellow Dr H Bayliss, and research supervisor. Once relevant articles were obtained and read, a database of references to use for the thesis was compiled.

1.2 BLOOD PRESSURE MEASUREMENT

1.2.1 History of blood pressure measurement

In 1628, William Harvey noted that when an artery is cut, the blood spurts out as if under pressure. In his seminal work, *De motu cordis* (Figure 1.1), Harvey proposed that the heart did not continuously produce blood, but circulated it around the body in one direction.[3]

Figure 1.1 Harvey '*De motu cordis.*'



10

EXERCITATIO
Anatomica,
DE MOTV CORDIS
ET SANGVINIS IN
ANIMALIBVS.

Caput Primum.

Cauſa, quibus ad ſcribendum Author permotus fuerit.

CVM multis viuorum diſſectionibus (vti ad manum dabantur) animum ad obſeruandum primũ appuli; quo cordis motus vſum, & vtilitates in animalibus per autopſiam, & non per libros aliorumque ſcripta inuenirem: Rem arduam plane, & difficultatibus plenam cõtinuo reperi, vt (cum Fracaſtorio) motum cordis ſoli Deo cognitum fuiſſe, penè opinarer. Nec enim quomodo Syſtole, aut Diaſtole fieret, nec quando, aut vbi dilatatio, & conſtrictio exiſteret, recte potui internoſcere, propter celeritatem ſcilicet motus qui in multis animalibus, ictu oculi, quaſi traiecto fulgure, ſe in conſpectum exhibuit, & ſubtraxit illico, ita vt modo hinc Syſtolen, illinc Diaſtolen, modo è contra, modo varios, modo confuſos fieri motus me exiſtimabam cernere: vnde animus mihi fluctuabat, nec quid vel ipſe ſtatuerem, vel aliis crederem habebam, & motum cordis eſſe qualis Euripi fluxus, & refluxus Ariſtoteli, Andream Laurentium ſcripſiſſe non mirabar.

Tandem maiori indies, & diſquiſitione, & diligentia vſus, multa frequen-

Figura 1.

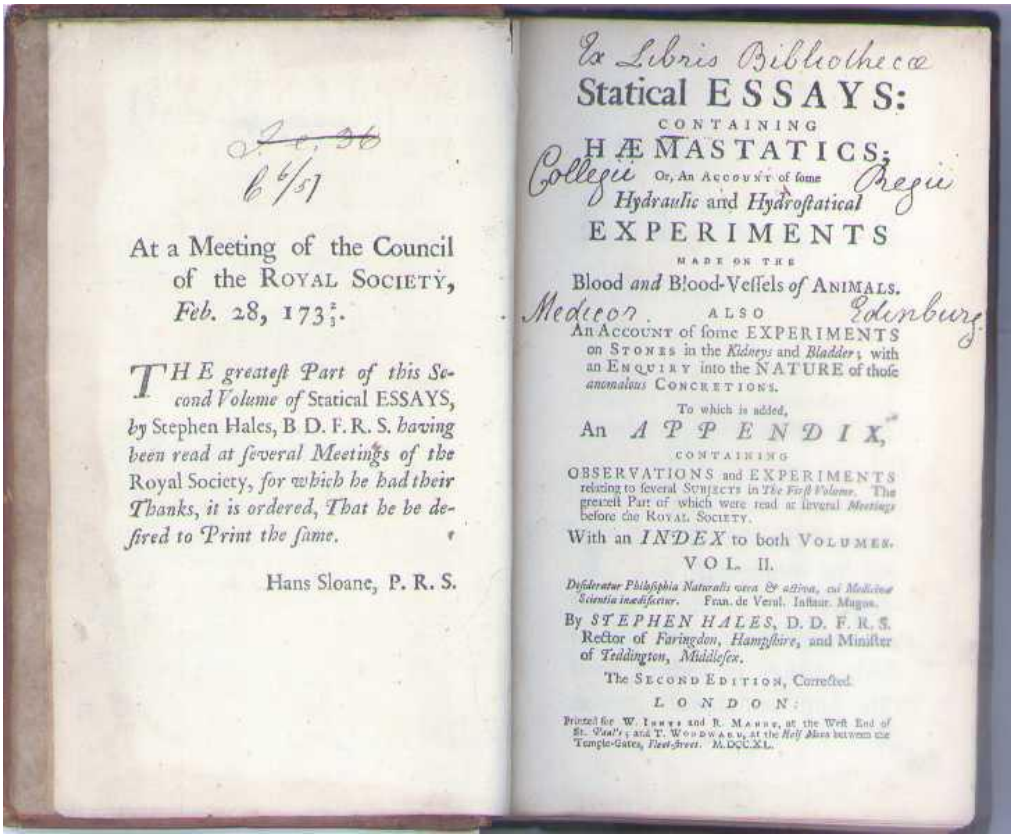
Figura 2.

Image by courtesy of the Royal College of Physicians of Edinburgh

In 1733, the Reverend Stephen Hales performed the first direct blood pressure measurement by cannulating the femoral artery of a conscious horse [4] (Figure 1.2). He described how 'in December I caused a mare to be tied down alive on her back…having laid open the left cruel artery about three inches from her belly, I inserted into it a brass tube whose bore was one sixth of an inch in diameter…to this I fixed a glass tube of nearly the same diameter which

was nine feet in length. Then, untying the ligature of the artery the blood rose in the tube to eight feet in length, three inches perpendicular above the level of the left ventricle of the heart.' The tubing was used to measure the mean pressure, its pulsatile nature, and changes due to respiration. Hales suggested human blood pressure would measure seven feet (176 mmHg). However, he ceased experiments quoting 'the disagreeableness of anatomical dissection.' [5]

Figure 1.2. Hales 'Statical (sic) Essays, containing haemastaticks'



At a Meeting of the Council of the ROYAL SOCIETY, *Feb.* 28, 173⅔.

THE greatest Part of this Second Volume of Statical ESSAYS, *by* Stephen Hales, B. D. F. R. S. *having been read at several Meetings of the* Royal Society, *for which he had their Thanks, it is ordered, That he be desired to Print the same.*

Hans Sloane, P. R. S.

Ex Libris Bibliothecæ Collegii Regii Medicor. Edinburg.

Statical ESSAYS:

CONTAINING

HÆMASTATICS;

Or, An Account of some *Hydraulic* and *Hydrostatical* EXPERIMENTS

MADE ON THE

Blood *and* Blood-Vessels *of* ANIMALS.

ALSO

An ACCOUNT of some EXPERIMENTS on STONES in the *Kidneys* and *Bladder*; with an ENQUIRY into the NATURE of those *anomalous* CONCRETIONS.

To which is added,

An *APPENDIX*,

CONTAINING

OBSERVATIONS and EXPERIMENTS relating to several SUBJECTS in *The First Volume*. The greatest Part of which were read at several *Meetings* before the ROYAL SOCIETY.

With an *INDEX* to both VOLUMES.

VOL. II.

Desideratur Philosophia Naturalis vera & activa, cui Medicinæ Scientia inædificetur. Fran. de Verul. Instaur. Magn.

By *STEPHEN HALES*, D. D. F. R. S. Rector of *Faringdon, Hampshire*, and Minister of *Teddington, Middlesex*.

The SECOND EDITION, Corrected.

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Image by courtesy of the Royal College of Physicians of Edinburgh

In 1828 Poiseuille was the first to use a mercury sphygmomanometer, measuring direct arterial pressure in a dog.[6] This reduced the height of the column by a factor of 13.6. The units for measuring BP (millimetres of mercury: mmHg) originate in this study. The first direct blood pressure measurement in a human was taken around 1850 when Faivre inserted a tube into an artery after amputation of an arm.[7] The impracticability of direct methods in a

clinical setting led to the development of indirect methods of blood pressure measurement. Ritter von Basch, an Austrian, invented the first sphygmomanometer which did not puncture the blood vessel. Initial systems used counter pressure on a distal artery, observing the pressure when the pulse distal to this disappeared and reappeared, loss and return of colour to the skin occurred, or appearance of oscillation in the mercury column.[8-10]

The arm-occluding cuff and mercury sphygmomanometer were described by Riva Rocci in Italy in 1896[11] and Hill and Barnard reported its use in the United Kingdom one year later.[12] The technique involved cuff inflation with recording of the pressures at which the palpated radial pulse disappeared and reappeared. However, it was not universally well received, with the British Medical Journal stating 'by using the sphygmomanometer we pauperise our senses and weaken clinical acuity.' [5] The final contribution to the modern technique of blood pressure measurement occurred when Korotkoff used a stethoscope, publishing the auscultatory method in 1905.[13]

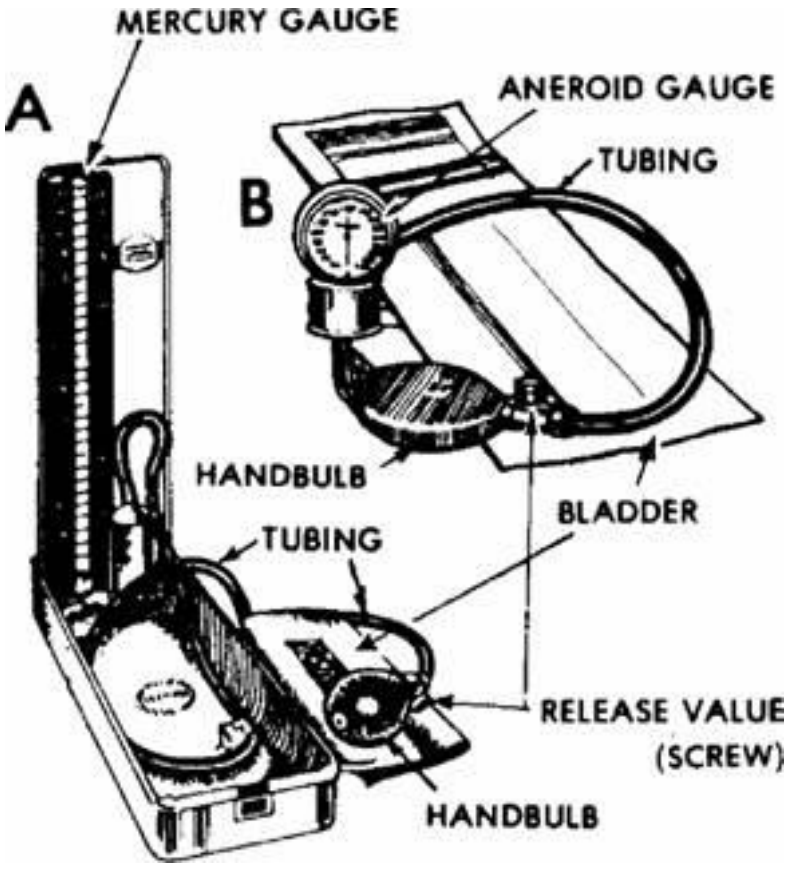
Doctors had assumed that high blood pressure occurred in eclampsia by the characteristic hard bounding pulse, and the availability of machines to measure blood pressure confirmed this in the late 19th century.[14] In 1874 Mahomed presented 'sphygmograms' from pregnant women, describing high 'tension' in the pulse returning to normal in one to three weeks.[15] Schedoff and Porockjakoff in 1884 also described high blood pressure with eclampsia,[16] and there followed an increasing number of reports of the measurement of blood pressure in pregnancy. Cook and Briggs used the Riva-Rocci sphygmomanometer at Johns Hopkins Hospital in 1903 to measure blood pressure in pregnancy, reporting raised readings preceding the onset of eclampsia.[17]

One of the first reliable longitudinal studies was carried out by MacGillivray et al in 1969.[18] They studied blood pressure throughout pregnancy in 226 primigravid women using the London School of Hygiene sphygmomanometer. Blood pressure was low in the first two trimesters and rose in the third trimester, with the highest levels occurring at six weeks postpartum. Increases in systolic pressure as pregnancy advanced were substantially less than those for diastolic pressure. They made several recommendations on standardisation of blood pressure measurement in pregnancy; however they did not make allowance for arm circumference, and used Korotkoff Phase IV for the diastolic pressure. These and other issues of blood pressure measurement technique are discussed below.

1.2.2 Blood pressure measurement today

Mercury and aneroid sphygmomanometers are commonly-used devices with similar features: a manually-operated inflation-deflation system connected by rubber tubing to an occluding bladder placed on the arm.[19] Inflation occurs with a bulb compressed by hand, and deflation using a hand-controlled release valve. The pump and control valve are connected to the sphygmomanometer by rubber tubing. The mercury reservoir is connected to a calibrated column where the blood pressure is read. In the aneroid sphygmomanometer, this is replaced by a more complex bellows and lever system and a 'clock-face' dial giving the reading.

Figure 1.3 Mercury and aneroid sphygmomanometers



There is concern about the possible toxic effect of mercury on the environment. In some European countries mercury is no longer permitted in hospitals and it is likely that this will become the case in the United Kingdom.[20, 21] Technical problems with cracked or perished rubber, and defective control valves making controlled pressure release difficult should be addressed with regular servicing of equipment. The aneroid manometer is vulnerable to damage over time with loss of accuracy, and should be regularly calibrated against a mercury sphygmomanometer.

Newer devices are now available which use oscillometric techniques. These calculate the blood pressure from changes in the amplitude of intra-oscillatory pressure waves, which are detected by the pressure cuff during deflation.[22] As the cuff deflates below the systolic blood pressure, blood begins to flow through the artery and a detectable vibration starts in the arterial wall. As cuff pressure falls below the diastolic pressure, blood flows easily and the vibrations cease. Detected vibrations are transferred through the cuff into a transducer in the monitor, which converts them into electrical signals, producing a digital readout. An oscillometric device is now available which measures blood pressure by detecting oscillations on inflation rather than deflation of a cuff.[23] There are also auscultatory monitors, which detect the Korotkoff sounds using an attached microphone in the pressure cuff.

Hundreds of blood pressure measuring devices are now available and these must be validated to set criteria to assess accuracy. The European Society of Hypertension has published recommendations in this area, including an international protocol.[24, 25] Validation standards have also been set by the US Association for the Advancement of Medical Instrumentation (AAMI) and the British Hypertension Society (BHS).[26, 27]

1.2.3 Possible sources of error

As well as the need for validation and regular maintenance of devices, there are other areas where errors may occur in BP measurement. The need to minimize these is paramount, as patients may undergo unnecessary investigations and receive medication which they do not need for many years, if readings are overestimated. Conversely, those needing further monitoring and treatment may be missed if readings are incorrectly thought to be in the normal range. Studies surveying staff measuring BP in pregnant women have shown considerable variation in practice.[28, 29] Table 1.1 illustrates the main sources of error in BP measurement. [6, 30-37]

Table 1.1. Sources of error in measurement of blood pressure using standard sphygmomanometer

Source	Notes
Variation due to intrinsic rhythms of respiratory fluctuation, periodic waves mediated by chemoreceptors, posture, external/internal factors (exercise, bladder distension, emotion, meals, tobacco, caffeine, alcohol, pain, temperature, and mental activity) & diurnal variation	BP is inherently variable: 80,000 to 140,000 tensions take place beat-to-beat over 24 hrs in a pregnant woman.
Equipment error: -Mercury -Glass tube -Air vent -Rubber tubing -Incorrect cuff size	Regular calibration and maintenance is needed -May leak causing underestimation of BP -Interior may be dirty due to oxidation of mercury, mercury can adhere giving overestimation of BP -Blockage due to clogging with mercury may inhibit entry of air when pressure released, upward drag on mercury when cuff deflated with overestimation of BP -Cracked/perished rubber: problems with deflation -If bladder too small pressure may not be fully transmitted to artery, giving overestimation. Use large cuff if mid-bicep arm circumference over 32 cm.
Observer bias: -Terminal digit preference -Threshold avoidance	 -Rounding BP to zero or five. In one study ~50% of values by clinic staff had terminal digit zero.[38] -Prejudice in favor of 'normal values', or to fit preconceived ideas
Observer error	Fatigue, poor memory/concentration/reaction time, impaired auditory/visual acuity can effect readings

Table 1.1. (cont.) Sources of error in measurement of blood pressure using standard sphygmomanometer

Source	Notes
Poor observer technique: -Poor patient posture and position of manometer -Incorrect rate of deflation -Incorrect interpretation of Korotkoff sounds	Recommendations: training of observers [35] -Patient sitting with arm supported at level of heart -Deflate at 2-3 mmHg per second -Use K5 (disappearance of sound), not K4 (muffling) [39, 40] and palpate to find systolic pressure to avoid auscultatory gap.
White-coat effect	Note distinction between white coat hypertension (see section 1.4), and white coat effect which can occur in people with established hypertension

The limitations of conventional BP measurement described in Table 1.1 have led to exploration of alternative methods. These include automatic blood pressure measurement devices and ambulatory blood pressure monitoring, which is discussed further in section 1.4 below.

1.3 HIGH BLOOD PRESSURE IN PREGNANCY

1.3.1 Classification

As outlined above, the diagnosis of hypertension depends on measuring blood pressure accurately. Pregnant women as a group have special characteristics, and must be considered separately. Blood pressure is the product of cardiac output and peripheral resistance. In pregnancy, reduction in systemic vascular resistance mediated by local factors results in a reduction of BP by 5-10 mmHg. In the third trimester the peripheral vascular resistance increases, and BP also rises towards term.[41] Pregnancy may be the first time a BP reading

has been taken, with no prior readings for reference. There may be pre-existing disease brought to light, or exacerbated by pregnancy, or hypertensive disease purely related to the pregnant state. There is a short window of time during the gestation when appropriate management must be instituted. The final diagnosis is confirmed only in retrospect when postnatal blood pressure is available. Therefore, definitions and classification of hypertensive disease in pregnancy must be clear and consistent.

Unfortunately, this has not been the case. Historically, research in hypertension in pregnancy has been dogged by variations in diagnostic thresholds for blood pressure and proteinuria, a plethora of classification systems and varied terminologies.[42] In large epidemiological population-based studies, ICD coding (International Classification of Diseases) in this 'vexing and enigmatic group of disorders' is notoriously unreliable: one study reported that one in four codings for pre-eclampsia was incorrect.[43]

An important and universally agreed change over recent years is the abandonment of oedema as a criterion for the diagnosis of pre-eclampsia. Also, relative increases of 15 mmHg and 30 mmHg diastolic BP (DBP) and systolic BP (SBP), respectively, are no longer recognized as defining hypertension by the relevant bodies in Australasia, the United States and the International Society for the Study of Hypertension in Pregnancy (ISSHP).[44-46] The same guidelines use a SBP $\geq$ 140 mmHg and/or a DBP $\geq$ 90 mmHg for the definition of raised BP in pregnancy. The use of absolute thresholds for 'abnormal' systolic and diastolic BP is not arbitrary; there is evidence supporting their use from studies of outcomes at different levels of BP.[47, 48] These cut-off points alert clinicians and patients to hypertensive disease and are established in clinical and research practice. Finally, the use of 'muffling' of sounds (Korotkoff IV) is no longer recommended, and Korotkoff V (disappearance of sounds), must

be recorded as the diastolic blood pressure.[39, 40] This removes important areas of potential for variation in research and practice that have confounded consistency and standardization.

Proteinuria is a classic prerequisite to diagnose pre-eclampsia, but the exact definition has varied.[49] A protein reagent dipstick placed in a random urine sample is widely used, measuring concentration of protein and vulnerable to error/variation due to contamination, specific gravity, pH, posture and observer error.[50, 51] A value of 1+ or more, which ideally correlates with a 24-hour urinary protein value of 300 mg in 24 hours, is considered abnormal. In a study of accuracy of dipstick techniques Waugh et al found the 1+ threshold had poor accuracy in predicting significant proteinuria as defined by 24-hour urine, and was of limited use.[52] Therefore although dipstick urine is widely used for initial assessment, the gold standard remains the 24-hour urine. There has been recent interest in the random urine protein/creatinine ratio. However, the wide variations in protein excretion hour-to-hour in pre-eclampsia have meant 'this test has not been universally endorsed for evaluating proteinuria when pre-eclampsia is suspected.' [49] It has however been recommended by ISSHP that the order of preference for urinalysis is 24-hour urine collection, followed by protein/creatinine ratio (cut-off 30 mg/mmol), and dipstick urine if it is the only test available.[46]

The definitions above are combined by ISSHP to give four main hypertensive disorders in pregnancy: gestational hypertension (isolated hypertension after 20 weeks), chronic hypertension (diagnosed before 20 weeks and/or not resolving postpartum), pre-eclampsia-eclampsia, and pre-eclampsia superimposed on chronic hypertension.[46] Clinical diagnosis of pre-eclampsia is defined as de novo hypertension after 20 weeks gestation with one or more findings, including proteinuria and several other clinical/laboratory parameters. For research

purposes proteinuria must be present and properly documented. This is consistent with recommendations that clinical definitions should be 'as loose as practical for patient safety, whereas research definitions should be stringent.' [37] The research definition and categories are based on those proposed in an important paper by Davey and McGillivray in 1988 and endorsed by ISSHP, which are used in this thesis.[53] All definitions must be used with the caveat that pre-eclampsia in particular is a complex maternal syndrome with varying presentations. Hypertension or proteinuria is reported as absent in 38% of women with eclampsia[54] and 10-15% of patients with HELLP syndrome.[55]

It is thus important to note that even an accurate assignation of 'diagnosis' simply signifies the woman meeting a 'definition' according to the clinical presentation alone. There are no reliable and specific disease markers. Research to establish the patho-physiology behind these disorders of pregnancy continues, and is vital to improve prediction of perinatal outcomes and optimise patient care. Hypertension in pregnancy has been aptly described as 'a disorder begging for pathophysiological support.' [56]

1.3.2 Incidence and implications of high blood pressure in pregnancy

Hypertensive disorders in pregnancy are consistently one of the top three causes of direct maternal mortality in both the United Kingdom and the United States, causing approximately 15% of maternal deaths and significant morbidity.[45, 57-59] Eclampsia, intracerebral haemorrhage and end-organ dysfunction all contribute to maternal morbidity and mortality. Ethnic origin and age are also relevant: in a 2001 report on mortality from pre-eclampsia/eclampsia in the United States, black women were 3.1 times more likely to die than white women, and women aged over 40 years were 5.3 times more likely to die than those aged 25-29 years.[60] Maternal deaths due to hypertension reach epidemic proportions in

developing countries, with death rates 100-200 times greater than Europe and North America.[61]

The overall reported rates of hypertension in pregnancy range from 6-10%.[45, 62, 63] Chronic hypertension occurs in 1-5% of pregnant women, with a higher incidence in women who are older, obese and of black ethnic origin.[64] The remainder have pre-eclampsia/eclampsia, which may be superimposed on chronic hypertension, and gestational hypertension.[45, 53] The rate of pre-eclampsia in the US increased by 40% between 1990-99, probably due to older mothers (with an increased rate of chronic hypertension) and more multiple pregnancies.[65]

Numerous studies have examined the effect of maternal hypertension on fetal outcome, with many demonstrating increased rates of pre-term delivery, growth restriction, and perinatal mortality.[66-87] Varied definitions of hypertensive disorders and perinatal outcomes lead to some difficulty in comparing results, but there is general consensus that women with pre-eclampsia, especially when superimposed on pre-existing chronic hypertension, have the worst outcomes. There is also evidence that racial factors are important in perinatal outcomes, with pregnancies in black women being at increased risk, particularly when chronic hypertension is present.[66, 76, 79, 88] A 2006 WHO study of 7993 pregnancies in 6 developing countries found 24% of perinatal deaths were secondary to hypertensive disorders, second only to preterm delivery.[89]

Much recent work in the area of hypertension in pregnancy has focussed on screening women for pre-eclampsia with the hope of preventing it and reducing adverse outcomes. As stated above, the underlying patho-physiology of pre-eclampsia is still unclear. There is consensus that there is inadequate trophoblast invasion, with poor placental perfusion,

general endothelial dysfunction, platelet and clotting system activation, and an abnormal immune response with inflammation.[90] Oxidative stress has been proposed as important, leading to trials of preventative Vitamins C and E, but early optimism has not been supported by randomized trials, and a systematic review confirmed the evidence available discouraged this treatment.[91] Similarly, initial hopes for anti-platelet agents, hypothesised to correct the imbalance between prostacycline and thromboxane, were not confirmed when large studies showed only modest reductions in adverse outcomes. However, analysis of individual patient data has suggested that the 10% reduction in relative risk of pre-eclampsia would be important at a population level, and use of prophylactic aspirin should be discussed with women at risk.[92]

Community screening for risk factors and early detection of pre-eclampsia is recommended, with better evidence now available.[93, 94] Uterine artery Doppler screening has also been investigated, possibly in conjunction with biochemical markers.[95] One important advance is in the now routine use of magnesium sulphate to prevent and treat eclampsia,[96] but there are still many areas of controversy and uncertainty in the management of hypertension in pregnancy.

1.4 AMBULATORY BLOOD PRESSURE MONITORING

1.4.1 Ambulatory Blood Pressure Monitoring: an overview

Interest in "ambulatory" medicine has grown during the last two decades. The driving force behind much of the change has been financial. However, the demonstrable cost benefit of outpatient monitoring and treatment might not be matched in terms of clinical benefit. It is

important that new techniques of monitoring be rigorously examined for clinical effectiveness as well as cost effectiveness.

The inconsistent relationship between degree of hypertension and associated complications was noted in the 1950s by Sokolow.[6] To investigate if clinic BP was equivalent to overall BP he used a home monitor designed by Remler, which was manually inflated. Reports of the technique of non-invasive ambulatory blood pressure monitoring (ABPM) appeared in 1962,[97, 98] and NASA developed a miniaturised version of the Remler device to record the blood pressure of astronauts. In 1966 Sokolow's group published an important study, the first to show that end-organ damage was more closely related to mean daytime ABPM measurements than office BP.[99] In the 1970s Thorton designed an automatic non-invasive monitor, which he later wore himself on an early Space Shuttle flight.[6]

National guidelines on managing hypertension now include the use of ABPM in non-pregnant patients.[100-102] Although clinic readings remain fundamental, they may not represent the true situation for three reasons: variability of BP with a small number of readings, poor technique (section 1.2.3) and the 'white coat effect.' [103] Overall there are several clinical areas where ABPM is recommended in general medical practice (Table 1.2)

Table 1.2. Clinical scenarios where ABPM is recommended in non-pregnant patients

Use	Notes
Identification of white-coat hypertension (see below)	Useful in newly diagnosed patients with no end-organ damage
Monitoring and adjustment of drug treatment, and any related side-effects	Timing of medication can be adjusted especially for morning 'surges',[104] and to minimise unwanted side-effects
Diagnosis of postural hypotension, investigation of syncope, episodic hypertension and resistant hypertension	Autonomic neuropathy and panic disorder can be diagnosed
Prediction of end-organ damage, cardiovascular events and mortality, including as related to nocturnal 'dip' [105-107]	Improved detection of high-risk patients allowing targeted intervention, better prediction demonstrated
Suspected observer error and bias	

In spite of national recommendations about the use of ABPM, there are still areas of uncertainty and difficulty. Acceptability of the technique is variable (10-25% of patients prefer not to repeat it due to 'inconvenience').[108] There is also lack of consensus on which measures should be used by the clinician. Several methods of analysis have been described of varying complexity including the blood pressure load (percentage of the area under the curve above certain limits), 'hyperbaric index' based on time-specified tolerance and prediction intervals,[109] a Bayesian approach using restricted cubic splines and heterogeneous within-subject variances,[110] analysis of Circadian rhythm by multiple-component analysis, [111] and chronobiological analysis using MESOR (midline estimating statistic of rhythm), amplitude and acrophase.[112] In clinical practice the mean 24-hour, and day and night systolic/diastolic BP are most often used.

For all these indices normal ranges are needed for different populations. Values in normal populations for ABPM data have been established, revealing readings to be lower than 'office' BP.[113] There is still some controversy surrounding levels of 'abnormal' ABPM, but generally <135/85 mmHg (day), <120/75 mmHg (night) and <130/80 mmHg (24 hours) are used as cut-off points for non-pregnant populations.[98]

As referred to in section 1.2.2, devices must be validated for use in varying clinical situations, as reviews of studies show only 'about two thirds of ABPM devices tested can be recommended.' [98] To pass a device needs to be given Grade A or B by British Hypertension Society (BHS) Guidelines,[24] and to be awarded a 'pass' by the American Association for the Advancement of Medical Instrumentation (AAMI) criteria.[26] The website www.dableducational.com has full details of guidelines, devices and their ratings, and there is more discussion below.

1.4.2 Review of ambulatory blood pressure monitoring devices used in pregnancy

The need for objective validation of ambulatory monitors has been referred to above. Relevant publications on device validation in pregnant women are presented in Table 1.3 below. The literature search to identify these studies is described in section 1.1.2. Where details are available in the publication they are included, but in some papers few details are available on (for example) the parity or gestation of women in the study, and descriptions such as 'mild hypertension' are not defined. See the end of section 1.4.3 for further discussion of this issue.

Table 1.3. Publications relating to ambulatory blood pressure devices used in pregnancy, grouped by monitor.

Reference First author Year	Monitor(s)	Study design	Sample size	Subjects	Description	Findings	Recommendation
114 O'Brien 1993	SpaceLabs 90207 monitor	Validation study	86	Normotensive pregnant women.	Accuracy assessed by British Hypertension Society (BHS) protocol & Association for the Advancement of Medical Instrumentation (AAMI) criteria vs mercury device	BHS 1990: Systolic: Grade A Diastolic phase V: Grade C AAMI: Systolic: passed Diastolic: failed	More information is needed on the performance of BP measuring devices in pregnancy.
115 Shennan 1993	SpaceLabs 90207 monitor	Validation study	98	Pregnant women with range of BP <130/80 to >140/100	Accuracy assessed by BHS protocol & AAMI criteria vs mercury device	BHS 1990: Systolic: Grade B Diastolic phase V: Grade B AAMI: passed criteria	Device accurate in determining systolic and diastolic blood pressure by BHS/ AAMI protocols in pregnancy.
116 Shennan 1996	SpaceLabs 90207 monitor	Validation study	30	Nulliparous pregnant women with severe pre-eclampsia (BP >170/110 and proteinuria >500 mg /24 hours)	Accuracy assessed by BHS protocol vs mercury device	BHS 1990: Systolic: Grade C Diastolic phase V: Grade C Added to reference 115 (same authors) grading remains B/B.	Within acceptable limits in severe pre-eclampsia. Recommend future studies include women with pre-eclampsia

Table 1.3. (cont.) Publications relating to ambulatory blood pressure devices used in pregnancy, grouped by monitor

Reference First author Year	Monitor(s)	Study design	Sample size	Subjects	Description	Findings	Recommendation
117 Brown 1995	SpaceLabs 90207 (oscillometric) monitor Accutracker II (auscultatory) monitor	Validation study using direct intra-arterial readings compared with both ABPM devices	39	Pregnant women in third trimester with mild hypertension (not defined).	SpaceLabs (25 women) and Accutracker (14 women) accuracy assessed by BHS protocol & AAMI criteria vs intra-arterial pressures as reference	-SpaceLabs: BHS 1993: Systolic: Grade D Diastolic: Grade D AAMI: Failed -Accutracker: BHS 1993: Systolic: Grade D Diastolic: Grade C AAMI: Failed	Poor gradings in both devices, but is similar to comparisons to mercury devices, 'does not mean devices are unsuitable for use in pregnancy'.
118 Franx 1997	SpaceLabs 90207 (oscillometric) Monitor Profilomat (auscultatory) monitor	Validation study	55	Pregnant women: -21 normotensive, -22 diastolic BP>90 -12 diastolic BP>90 & proteinuria >300mg/24 hours -2 in 1st trimester -9 in 2nd trimester -44 in 3rd trimester	SpaceLabs & Profilomat accuracy assessed by BHS protocol vs mercury device on all women	-SpaceLabs: BHS 1990: Systolic: Grade B Diastolic: Grade C -Profilomat: BHS 1990: Systolic: Grade B Diastolic: Grade C Large differences with mercury readings in individuals, which increased with BP.	Ambulatory devices need to be evaluated at the extremes of BP range where maternal morbidity is more likely.

Table 1.3. (cont.) Publications relating to ambulatory blood pressure devices used in pregnancy, grouped by monitor

Reference First author Year	Monitor(s)	Study design	Sample size	Subjects	Description	Findings	Recommendation
119 Brown 1998	SpaceLabs 90207 Monitor OMRON HEM 705 CP portable (non ABPM) device	Comparative study	79	Normotensive pregnant women 'at risk' of pre-eclampsia (undefined) or with 'mild hypertension' (undefined)	Three BP readings on each device averaged and compared with average of three readings on mercury device, tested with Student's paired t-test and Bland Altman plots.	SpaceLabs tended to overestimate systolic BP by mean of 11: Standard Deviation (SD) 8 and diastolic BP by mean of 5 (SD 7) mmHg. Considerable patient variability in accuracy.	Recommend if record a limited number of readings, must compare with mercury readings. Do note that ABPM devices are designed for usage over 24-hour period.
120 Livi 1998	SpaceLabs 90207 Monitor Takeda TM2420 model 7	Cohort study of reproducibility	159	Pregnant women gestation 6-39 weeks -95 normotensive -42 previous gestational hypertension -10 previous pre-eclampsia -12 hypertensive in current pregnancy	SpaceLabs (19 women) and Takeda (140 women) used over two consecutive 24-hour periods in hospital. Two periods compared using reproducibility index (2 x standard deviation of differences between individual means.)	At group level the mean observed differences were not significantly different except the first 2 hours of readings.	'High overall reproducibility' supports use of the technique.

Table 1.3. (cont.) Publications relating to ambulatory blood pressure devices used in pregnancy, grouped by monitor

Reference First author Year	Monitor(s)	Study design	Sample size	Subjects	Description	Findings	Recommendation
121 Natarajan 1999	SpaceLabs 90207 Oscillometric monitor QuietTrak auscultatory monitor	Validation study	37	30 pregnant women with pre-eclampsia (diastolic BP>90 and >2+ proteinuria) 7 women (3 postpartum) with severe pre-eclampsia on high dependency unit with pulmonary oedema	SpaceLabs and QuietTrak accuracy assessed by BHS protocol & AAMI criteria vs mercury device in women with pre-eclampsia. Also assessed vs intra-arterial readings in 6 women with severe pre-eclampsia: device failed in one woman, excluded.	SpaceLabs/QuietTrak: BHS 1993: Systolic BP: Grade D Diastolic BP: Grade D AAMI: both failed. Intra-arterial test: both underestimated systolic, mean arterial pressures, QuietTrak also underestimated diastolic pressures.	Neither monitor can be recommended for clinical use in women with proteinuric pre-eclampsia.
122 Tape 1994	QuietTrak monitor	Accuracy study against mercury device	59	Normotensive women at 13-26 weeks gestation	Assessed vs mercury device on all women. 7 readings in each subject, means compared. Not using recognised validation protocol.	94% systolic BP and 99% diastolic BP within 5 mmHg cf mercury readings.	Device accurately determined blood pressures during pregnancy.

Table 1.3. (cont.) Publications relating to ambulatory blood pressure devices used in pregnancy, grouped by monitor

Reference First author Year	Monitor(s)	Study design	Sample size	Subjects	Description	Findings	Recommendation
123 Modesti 1996	QuietTrak monitor	Validation study	30	Pregnant women	Accuracy assessed by BHS protocol and AAMI criteria vs mercury device	BHS 1993: Systolic: Grade A Diastolic: Grade A AAMI: passed.	Passed all ratings, acceptable to patients.
124 Penny 1996	Quiettrak monitor	Validation study	85	Pregnant women in BP groups as per BHS protocol. 28 in second trimester, 57 in third trimester.	Accuracy assessed by BHS protocol and AAMI criteria vs mercury device	BHS 1993: Systolic: Grade B Diastolic Grade B AAMI: 'narrowly failed.'	Recommend for use in pregnancy, noting Korotkoff V is measured, and accuracy at high BP levels may be reduced.
125 Clark 1991	TM-2420 monitor	Validation study	30	Pregnant women: 11-38 weeks gestation -2 chronic hypertensive, rest normotensive.	Accuracy assessed by AAMI criteria vs Hawksley random-zero sphygmomanometer.	AAMI: Passed	Reliable estimates of systolic and diastolic Korotkoff phase V BP in pregnancy
126 Franx 1994	Oxford medilog monitor	Validation study	32	Pregnant women in mid-trimester 10 hypertensive, including 8 with proteinuria	Accuracy assessed by BHS protocol and AAMI criteria vs mercury device	BHS 1990: Systolic: Grade C Diastolic: Grade C AAMI: passed criteria	Differences were found in performance of device between normotensive and hypertensive women.

Table 1.3. (cont.) Publications relating to ambulatory blood pressure devices used in pregnancy, grouped by monitor

Reference First author Year	Monitor(s)	Study design	Sample size	Subjects	Description	Findings	Recommendation
127 O'Brien 1995	SpaceLabs 90207 TM-2420	Overview of validation studies	N/A	Pregnant women: see individual entries in this Table.	Review of factors influencing validation of ABPM devices (all patient groups). Three pregnancy studies are quoted.	In pregnancy three studies are quoted: -O'Brien 1993[114] -Shennan 1993[115] -Clark 1991[125] First two fulfilled requirements, Clark study used random zero sphygmomanometer so results 'questionable'	Manufacturers of devices must be encouraged to have independent evaluation according to approved procedure.
24 O'Brien 2001	SpaceLabs 90207 Profilomat QuietTrak	Overview of validation studies	N/A	Pregnant women: see individual entries in this Table.	Review of current status of device validation and recommendations of the European Society of Hypertension. Only includes studies with strict adherence to BHS and AAMI protocols.	In pregnancy seven studies quoted: References 114-116, 118, 121,123,124 Only two of nine devices (QuietTrak [123] and SpaceLabs 90207 [115]) validated in pregnancy passed BHS and AAMI criteria.	Only devices with Grade A or B under BHS protocol and fulfilling AAMI criteria are recommended.

The aims of protocols to assess BP monitoring devices are to standardise validation with minimum standards of accuracy and performance, and allow comparison of devices. In 1990, O'Brien et al published the British Hypertension Society (BHS) protocol for the evaluation of automated and semi-automated BP measuring devices, with special reference to ambulatory systems.[128] In the USA, the Association for the Advancement of Medical Instrumentation (AAMI) had produced standards for these devices in 1987, but these were not published in a journal, and did not cover all aspects (eg interdevice variability and patient acceptability).

The BHS protocol has six phases: observer training, before-use interdevice variability assessment, in-use assessment, after-use interdevice variability assessment, device validation on 85 subjects with specific characteristics/range of BP, and report of evaluation. Grades vary from A to D, depending on the percentage of readings in the test which differ from the mercury standard by ≤5, 10, or 15 mmHg. For example, in the original protocol, for an A grade (the best), 80% of measurements have a difference of ≤5 mmHg from the standard and 95% have a difference of ≤15 mmHg. Initially, acceptable limits were not strictly defined, with a Grade C 'acceptable' according to Greer[129], although later publications suggest a minimum B/B grading for systolic and diastolic BP (see below). For the AAMI criteria of accuracy, the device should not differ from mercury readings by more than 5 mmHg (standard deviation 8 mmHg or less).

The latest versions of the BHS and AAMI protocols were published in 2001 and 2003 respectively.[24, 26] The revised BHS protocol further stipulated that systems must be validated in 'special groups' such as pregnant women, using a sample size of 30 people if already passed in the general population. Devices should achieve at least grade B for systolic and

diastolic blood pressures to pass. A 'questionable' recommendation can be given if evidence is inadequate. The joint criteria (AAMI and BHS) are used in most validation studies.

Table 1.3 (above) shows the results of validation and accuracy studies for ABPM monitors in pregnancy. The first published study of the TM-2420 monitor by Clark et al did not use the BHS/AAMI standards, but did conclude that the monitor was reliable.[125] In 1993, two papers assessed the SpaceLabs 90207 ambulatory device in pregnant women.[114, 115] The grades are shown in Table 1.3. The study by Shennan et al found a B/B grade and a pass for AAMI standards, and stated the device was accurate. In O'Brien et al's study the Grade C for diastolic BP and the failure of diastolic BP to pass the AAMI criteria suggest suboptimal performance. The authors themselves state the grade but not whether this is an overall pass or fail, and recommend further studies before assuming devices valid in non-pregnant individuals are accurate in pregnancy. Interestingly this paper is extensively cited as a validation study in many publications on ABPM in pregnancy.

In 1994, in a comparison of automated and auscultatory readings (not ABPM) in 40 normotensive and 17 pre-eclamptic primigravid women, Quinn found that automated BP measurement devices underestimated blood pressure in women with pre-eclampsia by up to 30 mmHg.[130] The concern is that oscillometric devices (including ABPM monitors) might be affected by changed haemodynamics in pre-eclampsia, with a reduction in vessel wall compliance. A further study of the SpaceLabs 90207 device in 30 women with severe pre-eclampsia showed a Grade C/C which the authors describe as within acceptable limits, as long as clinicians are aware of possible discrepancies between oscillometry/sphygomanometry.[116] Adding this group to the previous validation study by the same group maintained the grade B overall. An assessment of the Oxford monitor was

published by Franx in 1994, with Grade C in systolic and diastolic readings. Accuracy of the device was worse in women with hypertension.[126]

In a different approach in 1995, Brown et al compared the SpaceLabs 90207 and Accutracker II ABPM monitors with intra-arterial recordings.[117] Although results were poor, mercury devices also compared poorly. The study design and use of the BHS grading was strongly criticised in a letter by O'Brien,[131] but in their reply the authors justify the study as exploring the hypothesis that automated devices might have been superior to mercury sphygmomanometers. Although useful to know that both methods are equally inaccurate related to direct methods, the relevance of further comparisons with intra-arterial pressure is questionable for practical and ethical purposes.

In 1995, in a review of the topic, O'Brien et al noted that of 43 ABPM devices, only 18 were validated according to the BHS/AAMI criteria.[127] Of these only 9 fulfilled the accuracy protocols stated in the paper of BHS grade B/B and AAMI standard met. Deviations from the protocol were common, and the authors refer to 'pernicious practices' such as companies transferring validation between models. Three studies in pregnancy are discussed (all referenced in Table 1.3): two are described as fulfilling AAMI and BHS criteria. Of these two, Shennan 1993 does conclude that the device fulfils the criteria in hypertensive pregnant women.[115] The other study in normotensive pregnancy (O'Brien 1993) in fact failed the device by criteria on reference to the original paper.[114]

The SpaceLabs 90207 device was assessed again for accuracy by Brown et al in 1998, comparing to an OMRON portable self-initiated device and mercury measurements.[119] They found overestimation of BP by the ambulatory monitor. However, the authors state that the

ABPM device is designed to be used over 24 hours and high numbers of readings would improve data stability. The authors recommend comparison with mercury readings in individuals. In a 1996 paper, Modesti et al studied the Welch Allyn QuietTrak ambulatory monitor, an auscultatory device, and it passed BHS and AAMI standards.[123] Two years previously, Tape had compared the QuietTrak to mercury readings with reported good correlation, but without formal validation.[122] In 1996 Penny et al added a further relevant study of the QuietTrak device, which passed BHS but just failed AAMI protocols.[124] The authors suggest that the marginal loss in grading at higher levels, less than that in oscillometric measurement, might offer an advantage in women with severe pre-eclampsia as the auscultatory device is not affected by changes in vessel wall compliance.

Examining this hypothesis, Franx et al compared an auscultatory (Profilomat) and oscillometric (SpaceLabs 90207) device in normotensive, hypertensive and (mild) pre-eclamptic pregnancies.[126] They concluded that they were as accurate as each other, but conclusions could not be drawn for women with severe pre-eclampsia. They used the 1990 version of the BHS protocol to allow comparison with previous studies. Wide limits of agreement caused concern, with for example a Profilomat diastolic BP of 85 mmHg indicative of a level between 71-102 mmHg phase V diastolic BP on mercury measurement. Auscultatory (QuietTrak) vs oscillometric (SpaceLabs 90207) monitors were then compared in women with pre-eclampsia by Natarajan et al, who found that 'neither monitor can be recommended for clinical use in women with proteinuric pre-eclampsia.' [121] Both devices failed on all counts in this population, with underestimation of BP compared to both mercury and intra-arterial readings.

Franx et al also make the important point that all these validation studies are done on women who are static, although ambulatory monitors by definition are used in motion during usual daily activities. Practically speaking it would not be possible to perform regular sequential mercury readings under controlled conditions during normal activities, as the protocols for validation require. However, other practical aspects of ABPM can be examined, and Livi et al studied the reproducibility of measurements over consecutive monitoring periods.[120] Women (some of whom were hypertensive) were hospitalised but mobile, and they found high overall reproducibility between the two time periods, supporting increasing use of the technique.

In conclusion, it is important to interpret individual blood pressure measurements with care and confirm readings with mercury devices, still the 'gold standard.' It is also suggested that ambulatory devices should be used with caution (if at all) in women with pre-eclampsia. In the future, the development of continuous waveform analysis with a finger device is a promising area.[24] Inflationary oscillometry, achieving Grade B/A in a study of women with pre-eclampsia by Golara et al, may also be applicable to future ambulatory devices, with improved accuracy.[23]

In an update in 2001, O'Brien reviewed the latest data on device validation, with seven papers found.[24] As stated in Table 1.3 and the discussion above, nine formal validations of several ABPM devices in pregnancy are quoted, with only two studies of devices passing (SpaceLabs 90207 in Shennan et al 1993, and QuietTrak in Modesti et al 1996).[115, 123] One further study by Franx et al 1994 was not included in O'Brien's review; the device failed.[118] Most of the reports in the literature of ABPM in pregnancy use the SpaceLabs device. There are also two reports on women's experience of the device, described in Section 4.5.

The conclusions on validation on a small number of measurements contrast with positive findings of the clinical use of 24-hour ABPM in pregnancy in a selection of the research in this area, discussed in the next section.

1.4.3 Ambulatory blood pressure monitoring in pregnancy

Given the importance of blood pressure disorders in pregnancy (section 1.3.2), there has been interest in the place of ABPM in the pregnant woman. In 1971 Seligman used an automated device taking 5-minute readings over 24 hours in normotensive, chronic hypertensive and pre-eclamptic pregnant women, showing a nocturnal drop in BP which was blunted in pre-eclampsia.[132] Other groups confirmed the pattern of change in the diurnal variation in pre-eclamptic pregnancies, using automated rather than ambulatory equipment on hospitalised women at rest.[133, 134] In 1984 Rayburn studied self-measurement of BP in 59 pregnant women with chronic hypertension, showing significantly lower measurements at home and when the average of two readings was used.[135]

As automated ambulatory monitoring devices became available, investigators began studies of this new technology in pregnancy, to further explore the possibility that BP readings outside the clinic might be more accurate, and to study patterns of blood pressure during usual activity. It was also hoped that the use of ABPM might decrease sources of error in conventional BP measurement, as outlined above in section 1.2.3. Tables 1.4-1.9 summarise the main areas of research. The sections of National Guidelines and Specialist Society recommendations relating to ABPM use in pregnancy (Table 1.11) and overall conclusions of reviews of ABPM in pregnancy (Table 1.12) are also included.

The work done in this area initially focussed on establishing normal values and patterns of ABPM in pregnancy, with emphasis on the 24-hour variation in BP over time. For the first time multiple readings over day and night were available while a patient continued normal activity (Table 1.4). Frequently reported findings were the normal decrease in BP at night, known as ‘dipping’, and the rise of BP between the second and third trimester.

Table 1.4. Studies of normal values and patterns of ABPM in normal pregnancy

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
136	Margulies 1989	Cross-sectional	11	Normotensive pregnant women in third trimester.	Del Mar Avionics Pressurometer III in hospital, over 24 hours.	Sleep values significantly lower than awake, patterns similar to non-pregnant women in previous studies.	ABPM allows adequate diagnosis of hypertensive disease in pregnancy.
137	Clark 1991	Longitudinal	140	Primiparous normotensive women	TM2420 monitor used over 24 hours, ABPM at 18 & 28 weeks	Significant rise in mean waking Systolic BP (SBP) & Diastolic BP (DBP) between 18 and 28 weeks gestation, sleeping BP always significantly lower than waking values.	Normal BP pattern in pregnancy is a rise between 18 and 28 weeks even if no evidence of pre-eclampsia.
112	Cugini 1992	Longitudinal	30 +30	Primiparous normotensive pregnant women (n=30). Results compared to 30 non-pregnant women.	SpaceLabs 90207, ABPM in hospital at 8-10, 18-20, 32-34 weeks gestation. Analysed using noninferential and inferential biometry.	Values tend to increase during second and third trimesters. Compared to non-pregnant values, overall lowering in pregnancy of the mesor (midline estimating statistic of rhythm.)	The standard limits in the study are appropriate references for gestational BP monitoring.

Table 1.4. (cont.) Studies of normal values and patterns of ABPM in normal pregnancy

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
138	Contard 1993	Longitudinal	48	19 nulliparous and 29 multiparous women, singleton pregnancy, body mass index <27, no hypertension or diabetes.	SpaceLabs 90207 (n=22) Diasys 200 (n=26) ABPM at 3, 6 and 9 months gestation.	BP highest in day, lowest at night, lowest in first trimester, minimal increase before 9th month.	Reference values may help define an alteration in the level and/or Circadian variation of BP during abnormal pregnancies.
139	Halligan 1993	Longitudinal	106	'Caucasian' primigravid women normotensive at booking.	SpaceLabs 90207, ABPM at 9-16, 18-24, 26-32, 33-40 weeks gestation, and 6 weeks postpartum.	DBP was lowest at 18-24 weeks. Day & night BP rose significantly at 33 to 40 weeks. Postpartum DBP greater than at 9-16 weeks. Nocturnal BP preserved throughout	Study provides reference values for ABPM in healthy primigravid women.
140	Ferguson 1994	Cross-sectional	150 + 30	150 pregnant and 30 age- and weight-matched non-pregnant women. 172 White, 8 Black.	Accutracker II ABPM at 18-22 (n=50), 30-32 (n=50) and 36-38 (n=50) weeks gestation.	BP always lower at night. All indices elevated at 36-38 weeks compared to earlier, but not higher than non-pregnant. Normal mean BP curves established for each gestation.	ABPM is a useful tool for the measurement and treatment of BP abnormalities during pregnancy.

Table 1.4. (cont.) Studies of normal values and patterns of ABPM in normal pregnancy

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
141	Stella 1996	Longitudinal	192	'Healthy' pregnant women (20-42 years, 85 nulliparous and 107 multiparous).	SpaceLabs 90207 ABPM in hospital at 8-12, 20-28, 32-40 weeks gestation.. Also studied 132 pre-eclamptic women. 26 chronic hypertensive women (see next table).	All waking indices higher than sleep measurements. 24-hour mean BP decreased in third trimester. Range of normal pressure values for each hour of day across 3 trimesters.	Reference values may help to define alteration in Circadian rhythm and level of BP in pathological pregnancies.
142	Siamopoulos 1996	Longitudinal	22	Normotensive pregnant women aged 18-29. 1st trimester (n=9), 2nd trimester (n=9), 3rd trimester (n=4).	Profilomat ABPM in all women, 6 had ABPM at 12, 34 and 32 weeks gestation.	Levels lowest at night, rising in third trimester.	ABPM is a useful tool for the evaluation of BP variability during pregnancy.
143	Taylor 2001	Longitudinal	102	'Healthy' normotensive women booking before 14 weeks gestation.	SpaceLabs 90207 ABPM at <14, 19-22, 27-30, 35-37 weeks gestation and 5-9 weeks postpartum, & sleep diaries. Assessed 'non-dippers' (less than 10% decrease in mean arterial BP in sleep.)	'Non-dippers' were common (occurred in 1:3 women), status changed during pregnancy.	As 'non-dipping' is common and inconsistent in normal pregnancies is unlikely to be a useful predictor of pre-eclampsia.

Table 1.4. (cont.) Studies of normal values and patterns of ABPM in normal pregnancy

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
144	Ayala 2001	Longitudinal	205	Normotensive pregnant women, mean age 30 years, 112 nulliparous, 93 multiparous, <16 weeks gestation at recruitment	SpaceLabs 90207 ABPM for 48 hours on recruitment then 4-weekly until delivery. Chronobiology analysis to assess influence of parity and age.	Reference values independent of parity or age, depend on rest/activity and gestation	Reference thresholds can be developed as function of rest-activity cycle and gestation, independent of parity or age.
145	Hermida 2001	Longitudinal	235	Untreated white women with uncomplicated pregnancies, <16 weeks gestation at recruitment.	SpaceLabs 90207 ABPM for 48 hours on recruitment then 4-weekly until delivery. Chronobiology analysis.	Time-qualified tolerance intervals calculated, across gestation.	Upper limits were markedly below usual thresholds used to diagnose hypertension in pregnancy. This method may help improve prognosis and diagnosis.
146	Higgins 2002	Cross-sectional	933	'Healthy' normotensive primigravid White women at 18-24 weeks gestation.	SpaceLabs 90207 ABPM for 24 hours and compared in women in working group (n=245), not working (n=289), & not working on day of ABPM (n=399).	Significant independent relation between work and ABPM, and work with subsequent pre-eclampsia.	Findings suggest further studies are warranted in third trimester. Data may be important to allow optimal management of hypertension in pregnancy.

Researchers then turned to assessing ABPM patterns in hypertensive pregnancies (Table 1.5), suggesting that changes in diurnal patterns and establishing ABPM thresholds could help with diagnosis, management and treatment. The effect on the nocturnal dip, with some studies reporting a drop in the day-night difference in pre-eclampsia, was proposed as a potential screening method, as well as providing possible insight into the physiological changes of the disorder. In Halligan et al's study to establish normal values in 106 primigravid women, three of the four patients who developed pre-eclampsia had shown loss of nocturnal dip at 18-24 weeks gestation.[139]

Table 1.5. Studies of ABPM patterns in hypertensive pregnant women

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
147	Rath 1990	Cross-sectional comparative	36	Normotensive (n=17) and pre-eclamptic (n=19) pregnant women	SpaceLabs 90207 ABPM for 24 hours. Information from Shennan[6] and on-line abstract.	Normotensive women had significant nocturnal decline in BP. Women with pre-eclampsia had attenuated nocturnal fall in BP, some had an increase.	Hypertensive emergencies are more likely to occur at night; consider this when prescribing anti-hypertensive drugs.
148	Montan 1995	Prospective controlled	20	Women with pre-eclampsia admitted in 3rd trimester with BP >140/90 and proteinuria > 0.25 g/24 hrs.	SpaceLabs 90207 ABPM once for 24 hours, readings compared with conventional BP.	ABPM well-tolerated, reliable. Measurements comparable to conventional BP.	ABPM is likely to improve our understanding and clinical management of hypertension in pregnancy. May be suitable to assess anti-hypertensive drug use.
149	Halligan 1996	Cross-sectional comparative observational	48	Normotensive (n=24) and pre-eclamptic (ISSHP definition: n=24) pregnant women, mean gestation 35 weeks.	SpaceLabs 90207 ABPM to assess diurnal variation and BP.	Drop in day-night BP difference in pre-eclampsia inversely related to mean BP.	Blunting of day-night BP difference may be useful adjunctive measure of disease severity in pre-eclampsia.

Table 1.5. (cont.) Studies of ABPM patterns in hypertensive pregnant women

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
141	Stella 1996	Longitudinal comparative observational	350	-132 women with pre-eclampsia (BP >140/90,proteinuria >0.5 g/24 hrs), -26 women with chronic hypertension (BP >140/90 <20 wks) -192 'healthy' pregnant women.	SpaceLabs 90207 ABPM in hospital at 8-12, 20-28, 32-40 weeks gestation. NB: in pre-eclampsia, ABPM done at diagnosis and in the third trimester.	BP in hypertensive women remained higher in the day than the night, and was at least 20 mmHg higher than normal pregnancies at all times.	In hypertension in pregnancy ABPM can provide useful support for clinical decision-making and managing anti-hypertensive treatment. May reduce hospital stays and contain costs.
150	Ayala 1997	Longitudinal comparative observational	113	Recruited <16wks -71remained normotensive -28 women had gestational hypertension (BP >140/90) -14 women had pre-eclampsia (BP >140/90, proteinuria >0.3 g/24 hrs.	ABPM-630 Colin 48-hrs ABPM on recruitment then 4-weekly until delivery. Analysed with chronobiology techniques.	Differences in circadian rhythm-adjusted mean between normal & hypertensive pregnancies found in all trimesters. In hypertensive women BP is stable in 1st half of pregnancy then increases to delivery.	Non-invasive ABPM with chronobiometric methods for analysis offers new end points that allow early assessment of the risk of gestational hypertension and pre-eclampsia.

Table 1.5. (cont.) Studies of ABPM patterns in hypertensive pregnant women

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
151	Hermida 2000	Longitudinal comparative observational	202	Recruited <16 wks -124 remained normotensive -55 women had gestational hypertension (BP >140/90) -23 women had pre-eclampsia (BP >140/90, proteinuria >0.3 g/24 hrs.)	ABPM-630 Colin 48-hrs ABPM on recruitment then 4-weekly until delivery. Analysed with chronobiology techniques.	Circadian differences in normal/hypertensive pregnancies: new end points for management	Differences in BP between healthy and complicates pregnancies can be seen in the first trimester. These new end points could lead to early identification of hypertension in pregnancy allowing early prophylactic intervention.
152	Brown 2001	Prospective double-blind cohort	186	158 women in third trimester successful monitoring: -63 pre-eclampsia -68 gestational hypertension -27 essential hypertension (Definitions as Brown 2000[44])	SpaceLabs 90207 ABPM on recruitment, results unavailable to patients or treating clinicians to reduce bias.	Sleep hypertension common, especially in pre-eclampsia,	ABPM can select a group of hypertensive pregnant women with elevation of night BP as a manifestation of overall raised BP, predominantly occurring in pre-eclampsia.

Table 1.5. (cont.) Studies of ABPM patterns in hypertensive pregnant women

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
110	Lambert 2001	Retrospective data analysis	206	Hypertensive (BP >140/90) pregnant women over 20 weeks gestation Selects data from Penny 1998 [153] (Table 1.7) with at least 10 daytime and 5 night readings.	SpaceLabs 90207 ABPM performed once.	Heterogeneity found in the within-subject variances, allowing for this impacts little on the model estimates of mean profiles.	Bayesian approach to analysis is a powerful way to analyse ABPM data. Within-subject variances can be modelled.
154	Walker 2002	Cross-sectional comparative	40	-20 normotensive pregnant women -20 hypertensive pregnant women: 9 gestational 8 pre-eclamptic 3 chronic hypertensive (Definition as Brown 2000[44]) All in third trimester	SpaceLabs 90207 ABPM on all patients once as an inpatient and once in hospital.	For women on antihypertensive treatment, ABPM varied between home & hospital settings	Hospitalisation does not significantly lower BP in pregnant women as a group, but differences for women on medication means women are at risk of under or over treatment if conventional BP is used.

However, further studies of ABPM as a 'screening' test for hypertension (particularly pre-eclampsia), were mostly disappointing, particularly in normal pregnancies, with low positive predictive values (Table 1.6). Although Kyle et al found women who developed pre-eclampsia had some raised indices, the maximum positive predictive value quoted was 45% with a sensitivity of 53%.[155] The use of the nocturnal 'dip' has also been questioned: Taylor showed 'nondippers' were common and the status changed during pregnancy (Table 1.4).[143]

In a large study of 1102 primigravid women, Higgins et al showed the best predictor for pre-eclampsia (24 hour mean diastolic BP of 71 mmHg) had a sensitivity value of 22% and a positive predictive value of 15%.[156] This study is cited as 'conclusive evidence that mid-trimester ABPM in a healthy primigravid population is not a clinically useful predictor of hypertension later in the pregnancy.' [32] One group has performed complex chronobiological calculations on blood pressure series in pregnancies, and reported very high sensitivities and specificities for this method in predicting hypertensive outcomes.[157, 158] However, this method is not currently widely used. Diabetic women, who have an increased risk of hypertensive complications of pregnancy, have been identified as a group where ABPM screening may be useful.[159, 160]

Table 1.6. Studies of ABPM as a screening test/predictor of hypertension in pregnancy.

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
155	Kyle 1993	Prospective interventional	145	Normotensive nulliparous women recruited at booking, mean age 28 years. Originally 161 recruits: 145 had data for awake ABPM vs clinic reading analysis, 127 had data for 24 hour analysis	TM2420 ABPM at 18 & 28 weeks. Primary outcome: pre-eclampsia. NB definition is not standard: Diastolic BP (DBP) increase of 25 mmHg to 90 or more, not all had proteinuria. Rate of pre-eclampsia 17/145=11.7%.	Awake systolic and mean arterial pressure (MAP) significantly raised in women with pre-eclampsia at 18 & 28 weeks; with diastolic BP at 28 weeks. With MAP ≥85 at 28 wks, sensitivity 65%, positive predictive value (PPV) 31%. Adding heart rate ≥90 bpm: PPV 45%.	2nd trimester ABPM was raised when pre-eclampsia arises, but predictive values are low, limited use. Adding heart rate increases efficiency; may be of clinical value if effective prevention at 28 wks is found.
156	Higgins 1997	Prospective interventional	1048	Healthy primigravid women recruited from antenatal clinic, all White. Originally 1102 recruits, 1048 had data for analysis.	SpaceLabs 90207 ABPM at 18-24 weeks. Primary outcome: pre-eclampsia (rate 23/1048= 2.2%) Secondary outcome: gestational hypertension (rate 64/1048=6.1%) Definitions standard: Davey & McGillivray[53]	Significantly higher ABPM in hypertensive groups compared to normotensive. Best predictor of pre-eclampsia: mean DBP ≥71 mmHg: sens 22%, PPV 15%	ABPM in a healthy primigravid population, at 18-24 weeks is not a useful predictor of hypertension

Table 1.6. (cont.) Studies of ABPM as a screening test/predictor of hypertension in pregnancy

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
161	Hermida 1997	Prospective interventional	113	'Caucasian' women <16 weeks at recruitment, -71 'healthy' pregnant women -28 developed gestational hypertension -14 developed pre-eclampsia	ABPM-630 Colin 48-hrs ABPM at recruitment & 4-weekly to delivery. Primary outcome: pre-eclampsia (definition: gestational hypertension + proteinuria >0.3g/24 hrs.) Secondary outcome: gestational hypertension (new BP>140/90)	Considerable overlap in 24 hour mean distribution in normotensive/hypertensive women. PPV <55% for any variable in any trimester.	24-hr mean is not useful to predict pre-eclampsia or gestational hypertension.
157	Hermida 1998	Prospective interventional	152	'Caucasian' women <20 weeks at recruitment, -92 'healthy' pregnant women -42 developed gestational hypertension -18 developed pre-eclampsia	ABPM-630 Colin 48-hrs ABPM at recruitment & 4-weekly to delivery. Primary outcome: pre-eclampsia (definition: gestational hypertension + proteinuria >0.3g/24 hrs.) Secondary outcome: gestational hypertension (new BP>140/90)	'Hyperbaric index' (total area of patient's BP above upper limit of tolerance interval for Circadian variability) calculated. Identified subsequent pre-eclampsia/gestational hypertension, PPV above 96% for all trimesters, 100% in third trimester.	Using the 'tolerance-hyperbaric test', ABPM, preferably at booking, provides sensitive end points for early risk assessment and a guide for preventative intervention in high risk pregnancy.

Table 1.6. (cont.) Studies of ABPM as a screening test/predictor of hypertension in pregnancy

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
162	Benedetto 1998	Prospective interventional	180	Women at high risk of pre-eclampsia or fetal growth restriction. -90 who had abnormal uterine artery Doppler scan (resistance index ≥0.58 at 20-22 wks.) -the next 90 with normal Doppler	SpaceLabs 90207 ABPM at 20-24 wks. Primary outcome: pre-eclampsia and pregnancy induced hypertension (PIH) (Definition standard: Davey & McGillivray[53]) Secondary outcome: fetal growth restriction (birth weight <10th centile)	Using midline estimating statistics of rhythm (MESOR) above cut-off value 111/68 mmHg, abnormal uterine artery Doppler + raised ABPM gave sensitivity of 58% & PPV 63% for PIH and pre-eclampsia (not assessed separately) Fetal growth restriction: sensitivity 30%, PPV 20%	This two-stage test of ABPM on women with abnormal uterine artery Doppler in high-risk women 'might indicate' women at risk of PIH or pre-eclampsia.
159	Flores 1999	Prospective interventional	32	-22 normotensive type 1 diabetic women -10 pregnant nondiabetic women All <10 weeks gestation.	SpaceLabs 90207 ABPM at 7-12, 20-24, 30-34 weeks gestation.. Primary outcome: pregnancy induced hypertension (PIH)=pre-eclampsia & gestational hypertension together. (Definitions standard: Davey & McGillivray[53])	'PIH' occurred in 8 (36%) of diabetic women and 1 (8%) control. In diabetics, receiver operator curves showed nocturnal SBP >105 mmHg in 2nd trimester best predictor for 'PIH': sensitivity 85%, PPV 87%.	ABPM may be useful in screening for PIH in pregnant diabetic women.

Table 1.6. (cont.) Studies of ABPM as a screening test/predictor of hypertension in pregnancy

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
160	Lauszus 2001	Prospective interventional	151	Type 1 diabetic women. Originally 185 recruits, data available on 151. Sensitivity and specificity calculated for the 87 primiparous women	SpaceLabs 90207 ABPM at 13, 25, 33 weeks gestation and 3 months post partum. Primary outcome: Pre-eclampsia (definition: new DBP ≥90 mmHg, proteinuria >0.3g/24 hrs).	ABPM was higher from 1st trimester onwards in women with pre-eclampsia. 25 (29%) of primiparous subjects had pre-eclampsia. Best predictor was daytime BP >122/74: sensitivity 68%, PPV 47%.	ABPM is a 'reliable' measurement for prediction of pre-eclampsia in primiparous women with insulin dependent diabetes.
158	Hermida 2001	Prospective interventional	328	All<16 weeks gestation -205 remained normotensive -92 women developed gestational hypertension -31 women developed pre-eclampsia	SpaceLabs 90207 48-hrs ABPM at recruitment & 4-weekly to delivery. Primary outcome: pre-eclampsia (definition: gestational hypertension + proteinuria >0.3g/24 hrs) and gestational hypertension (new BP>140/90 after 20 wks)	For pre-eclampsia and gestational hypertension combined, threshold Systolic BP (SBP)/MAP/ DBP of >130/100/80 (day) and >110/85/70 (night) gave best results: sensitivity 78% and PPV 64%.	'Blood pressure load' (percentage of values above a given reference limit) is a good predictor of 'hypertension in pregnancy'. NB: lower limits than conventional BP.

Table 1.6. (cont.) Studies of ABPM as a screening test/predictor of hypertension in pregnancy

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
163	Brown 2001	Prospective single-blind comparative cohort	286	-122 pregnant women at risk of pre-eclampsia -164 pregnant women at 'usual risk' for pre-eclampsia Mean gestation 25 weeks.	SpaceLabs 90207 ABPM at 18-30 weeks while normotensive (BP<140/90, no pre-eclampsia). Results unavailable to clinicians to reduce bias. Primary outcome: combined pre-eclampsia/ gestational hypertension (Definitions as Brown 2000[44])	Primary outcome in high risk group: 55 (45%) usual risk group: 13 (8%) Both groups: ABPM higher in women developing hypertension Best predictors: usual risk group 24-hr SBP ≥115 mmHg (sensitivity 77%) High risk group sleep DBP ≥62 (sensitivity 70%)	In high and normal risk women raised ABPM is related to pre-eclampsia, but with low sensitivities
164	Tranquilli 2004	Prospective interventional	334	Normotensive non-proteinuric nulliparous pregnant women	SpaceLabs 90207 at 20 wks gestation. Primary outcome: pregnancy induced hypertension 'PIH' (pre-eclampsia/gestational[45]) Secondary outcome: fetal growth restriction (weight <5th centile)	Analysed with chronobiology. PIH in 33 (10%) For both outcomes ABPM 24 hour DBP mean was significantly higher. Most effective threshold is 68 mmHg for hypertension (PPV 89%), 67 mmHg for growth restriction (PPV 61%).	ABPM at 20 weeks in primigravida 'reliably predicts' idiopathic IUGR and PIH, using 24 hour diastolic mean.

Other women who are high-risk for pre-eclampsia, especially those with chronic or gestational hypertension, have also been investigated as a group for the predictive value of ABPM for maternal and fetal outcome (Table 1.7). Here the results have been more encouraging when ABPM is compared to conventional BP recording. Prospective observational studies have suggested ABPM is superior to conventional methods in predicting proteinuria in women with new hypertension after 20 weeks gestation.[165] Peek et al showed ABPM in 109 nulliparous hypertensive women improved identification of patients at high risk of poor obstetric outcome (caesarean and preterm delivery, admission to neonatal unit, and proteinuria).[166] However, a larger study of 348 women showed the only outcome where ABPM was superior to day unit BP was severe hypertension within two weeks.[153]

In a prospective cohort study Bellomo et al classified a subset of women with raised conventional BP and normal ABPM as having white coat hypertension, (WCH). In 144 women with hypertension in the third trimester, 42 (28%) had WCH.[167] The remaining women with 'true' hypertension had significantly higher rates of pre-eclampsia (61.7% 'true' vs 7.1% WCH), longer hospital stay, lighter babies and shorter pregnancies compared to normotensive controls and women with WCH. Interestingly the caesarean rate was similar in WCH and 'true' hypertensive groups (45.2% vs 41.1%), but significantly lower in normotensives (12.4%). The authors suggest this may reflect influence of conventional BP on clinical decision-making. One limitation to this study is that ABPM was only performed once and patients were admitted to hospital the day before performing the test. However the method used seemed to identify a group of women with WCH and significantly lower associated risk.

Bar also reported a high rate of WCH (62%) in women presenting with raised conventional BP in the second trimester, with associated decreased risk of pre-eclampsia, preterm delivery and growth restriction. [168] The issue of white coat hypertension is discussed below.

Four further papers have looked specifically at fetal growth and birth weight (Table 1.7), with Waugh et al showing ABPM to be the best predictor of fetal growth in women with non-proteinuric hypertension. In a prospective observational study of 237 women (mean gestation at referral 35.6.weeks) there was an associated fall in birth weight of 68.5g for every increase of 5 mmHg in daytime mean DBP, but day-unit measurements showed no association.[169] Churchill et al reported similar correlation in a study of 209 healthy nulliparous women, with a 5 mmHg increase in mean 24-hour DBP at 28 weeks gestation associated with a 68g decrease in birth weight, and a 76 g decrease at 36 weeks gestation, using multivariate analysis.[170]

Maggioni et al used chronobiology techniques to show a larger Circadian amplitude of DBP on ABPM was associated with growth restriction (< 10^{th} centile) in normotensive women.[171] However, an inverse relation between the Circadian amplitude of SBP and fetal growth restriction was seen in hypertensive women, possibly related to compensatory mechanisms in hypertensive women. Only 19 women had IUGR overall in the study, with five having 'pregnancy-induced hypertension' so limited conclusions can be drawn from this paper. Finally, Tranquilli et al showed that 139 women with growth restricted babies who were normotensive by conventional BP, had significant higher ABPM measurements compared to a control group with normal fetal growth.[172] The authors state that these higher levels in the normal range may still influence (or be the consequence of) altered uterine and placental perfusion, and ABPM can be used to aid investigation for women with small babies.

Table 1.7. Studies of ABPM as a predictor of perinatal outcome in hypertensive pregnancies

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
166	Peek 1996	Prospective observational	109	Nulliparous white women with BP at least 140/90 after 20 weeks gestation. (mean gestation 35 weeks).	SpaceLabs 90207 ABPM vs mean of 6 conventional readings 30 minutes apart on day unit. Outcomes: proteinuria, delivery <37 weeks, birth weight <10th centile, neonatal unit admission, Caesarean	With Diastolic BP (DBP) >90 mmHg, relative risk with ABPM greater than conventional: Proteinuria p=0.034 Preterm delivery p<0.001 Low birth weight p=0.001 Neonatal Unit (NNU) admission p=0.001 Caesarean delivery p=0.007	ABPM appears to improve the identification of patients who are at high risk of poor obstetric outcome, and is worthy of further evaluation.
173	Engfeldt 1996	Prospective observational	20	-12 women with untreated chronic hypertension (BP>140/90 in 1st trimester or known chronic hypertension) -8 normotensive women	SpaceLabs 90207 ABPM at 8-14, 19-23, 34-36 weeks and 3 months postpartum Primary outcome: superimposed pre-eclampsia (definition proteinuria ≥2+ dipstick, or >0.3 g/24hours)	3 women (25%) developed pre-eclampsia. No consistent pattern in ABPM. In both groups nocturnal 'dip' was absent in 6 women on at least one reading.	In women with chronic hypertension, absent nocturnal dip was of no value in predicting pre-eclampsia.

Table 1.7. (cont.) Studies of ABPM as a predictor of perinatal outcome in hypertensive pregnancies

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
165	Halligan 1997	Observational study	48	Primiparous women presenting with hypertension (mean of ≥140/90 on 5 readings 30 minutes apart) at >20 wks gestation. Mean gestation 35.5 wks	SpaceLabs 90207 ABPM vs conventional BP (CBP) on the day unit: mean of 5 readings 30 minutes apart (Korotkoff 4) Outcome: 24-hour urine proteinuria levels	On regression analysis day-time (p=0.026) and night-time (p=0.004) ABPM had significant positive relation with log proteinuria. No conventional parameters reached statistical significance.	ABPM gives better information on disease status in pre-eclampsia (assessed by proteinuria) than conventional BP measurement
170	Churchill 1997	Prospective observational	209	Nulliparous women (86% of 244 consecutively referred women meeting criteria of study: excluding medical disorders, twin pregnancy.) Eight infants delivering <32 wks were excluded.	SpaceLabs 90207 ABPM at 18 (n=209), 28 (n=202) and 36 weeks (n=179) gestation. Outcomes: birth weight, ponderal index, head circumference.	In multivariate analysis, diastolic ABPM at 28 and 36 weeks were inversely associated with birth weight. Diastolic ABPM at 28 weeks was a significant predictor of head circumference at birth.	There is a continuous inverse relationship between maternal BP and birthweight in nulliparous women.

Table 1.7. (cont.) Studies of ABPM as a predictor of perinatal outcome in hypertensive pregnancies

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
153	Penny 1998	Prospective observational study. Clinicians blinded to ABPM results.	348	Women >20 wks gestation with BP ≥140/90 not on anti-hypertensive treatment. 270 were fully compliant with ABPM, analysis done on all 348 women.	SpaceLabs 90207 ABPM vs mean of up to 5 BP measurements 30 minutes apart. Outcomes birth weight <3rd centile, preterm delivery, NNU admission. BP >160/110, proteinuria (>500 mg on 24 hour urine or 2+) in 2 weeks & overall.	With threshold of 135/85, ABPM had increased sensitivity & decreased specificity for all outcomes except systolic BP & proteinuria. ABPM predicted severe hypertension within 2 weeks significantly better than CBP	ABPM may reduce inpatient antenatal admissions, and may allow better risk assessment. A randomised controlled trial was proposed.
167	Bellomo 1999	Prospective cohort study.	247	-144 women with BP>140/90 (mean of 3 readings 5 minutes apart). Subdivided: 102 'true' and 42 white coat hypertension (WCH) -103 normotensive women. All at gestation 26-38 wks.	TM 2420 ABPM on all. WCH defined: office BP ≥ 140/90 with ABPM below departmental reference ranges. Outcomes of pregnancy duration, pre-eclampsia (proteinuria >0.3 g/24h) caesarean, placental & neonatal weight, Apgars & hospital stay compared in 3 groups.	Shorter pregnancy duration, more pre-eclampsia, lower birth weight & longer neonatal stay were seen in the true hypertension group vs the other two (all p <0.001). Caesarean rates were similar in WCH & true hypertension; in both groups rates were higher than controls.	In women with elevated BP in the third trimester, ABPM is better than office BP (distinguishing true hypertension from WCH) in predicting outcomes (pre-eclampsia, early delivery, birth weight).

Table 1.7. (cont.) Studies of ABPM as a predictor of perinatal outcome in hypertensive pregnancies

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
168	Bar 1999	Prospective cohort study. Clinicians blinded to ABPM results.	60	60 women at 14-28 wks gestation with at least two BP readings ≥140/90 30 minutes apart . Subdivided: 23 women with 'true' and 37 with white coat hypertension (WCH).	SpaceLabs 90202 ABPM. WCH defined as office BP ≥140/90 with ABPM daytime mean below 135/85. Outcomes: pre-eclampsia, growth restriction, preterm delivery	Pre-eclampsia (p=0.005), growth restriction (p=0.014), & preterm delivery (p=0.01) were significantly more likely in the 'true' hypertension group.	2nd trimester ABPM differentiates WCH (rate of 62% in this study) with associated better pregnancy outcomes compared with 'true' hypertension.
169	Waugh 2000	Prospective observational study	348	Pregnant women >20 wks gestation, office BP ≥140/90. 111 excluded (proteinuria), 3 excluded (missing data). ABPM data in 184 (daytime) & 151 (nighttime).	SpaceLabs 90207 on all women. Women with proteinuria (>0.3 g/24 hrs or 2 consecutive urine dipstick readings ≥1+) were excluded. Primary outcome: birth weight.	A significant inverse association found between daytime ABPM and birth weight: an increase in 5 mmHg associated with birth weight fall of 68.5 g. Remained after adjusting for confounders. No association between day unit BP and birth weight.	Evidence that maternal BP may be important variable in the association between birth weight and subsequent adult hypertension.

Table 1.7. (cont.) Studies of ABPM as a predictor of perinatal outcome in hypertensive pregnancies

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
174	Hermida 2002	Prospective cohort study. Clinicians blinded to ABPM.	444	Women <16 wks gestation in a tertiary unit. 41 withdrew.5 groups: -high office & high ABPM n=65 -normal office, high ABPM n=63 -both normal n=222 -high office,normal ABPM n= 13 -pre-eclampsia: both high, proteinuria n=40	SpaceLabs 90207 ABPM over 48 hours at recruitment & monthly. Hyperbaric index used. Proteinuria defined as >0.3 g/24h.	Unlike average office BP, the hyperbaric index was significantly higher in pre-eclampsia. Normotensive women as defined by ABPM had better outcomes (birth weight, preterm delivery, Caesarean section)	'Hyperbaric index' derived from ABPM is markedly superior to office measurements for diagnose 'true gestational hypertension' & predict pregnancy outcomes.
171	Maggioni 2005	Prospective observational study.	52	Women in third trimester. -33 uncomplicated pregnancies -19 with growth restriction confirmed at birth	SpaceLabs PA 2500 ABPM. Growth restriction defined as birth weight $<10^{th}$ centile. Five women in each group had raised BP (>140/90 mmHg).	The circadian amplitude of diastolic BP was larger in fetal growth restriction (chronobiology used). The finding persisted in separate analysis of normotensive women.	The circadian amplitude of diastolic BP, already known to be associated with risk of stroke and shortened lifespan, is related to fetal growth restriction.

Table 1.7. (cont.) Studies of ABPM as a predictor of perinatal outcome in hypertensive pregnancies

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
172	Tranquilli 2005	Prospective cohort study. Clinicians blinded to ABPM results.	279	-139 women with fetal growth restriction -140 normotensive women matched for age & gestation (32-34 weeks) without fetal growth restriction. All primigravid.	SpaceLabs 90207 ABPM in all women. Growth restriction defined as birth weight $<10^{th}$ centile, corrected for gender.	Normotensive pregnant women with fetal growth restriction had significantly raised ABPM compared to control group ($p<0.0001$).	Even in the absence of overt hypertension, pregnant women with growth restricted babies have blood pressure higher than normal. ABPM can aid accurate evaluation of idiopathic non-genetic intrauterine fetal growth restriction.
87	Giannubilo 2006	Prospective cohort study.	423	-223 pregnant women with 'mild chronic hypertension' (BP ≥140/90 twice 4 hours apart) -200 controls matched for age & parity	SpaceLabs 90207 ABPM (1^{st}, 2^{nd}, 3^{rd} trimester, post-partum, 6 wks post partum). Doppler of uterine arteries at 24 weeks gestation. Outcome: superimposed pre-eclampsia (new proteinuria >0.3 g/24 hrs/uncontrolled BP/ abnormal liver function).	Mean ABPM was significantly higher in cases vs controls. Mean ABPM at 24 weeks (threshold of 121/78) is of most prognostic value for predicting superimposed pre-eclampsia.	In women with chronic hypertension in the second trimester, ABPM and uterine artery Doppler velocimetry are able to detect those at risk of superimposed pre-eclampsia.

Although reviews (see below) often quote the study of anti-hypertensive medication as an area where there is a possible role for ABPM, only one study was found in the literature review (Table 1.8). Neri suggested ABPM was an effective and reliable method, in a study comparing glyceryl-trinitrate and oral nifedipine.[175] ABPM has also been used as a research tool in assessing effects of combined spinal epidural anaesthesia and antenatal thyrotrophin releasing hormone on blood pressure.[176, 177] The use of repeated measurements with the technique allowed for smaller sample sizes in these studies.

Table 1.8. Studies of ABPM to evaluate anti-hypertensive medication or as a research tool

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
176	Shennan 1995	Prospective observational	62	Women in labour using combined spinal epidural (CSE) analgesia.	SpaceLabs 90207 ABPM done before and following procedure with readings every 10 minutes, increased to 5 minutes at spinal injection. One reading was taken post partum.	ABPM showed a significant fall (>20%) in systolic BP in 8 women on administering the spinal injection. 52 women received an epidural dose and none had significant hypotension.	Combined spinal epidural analgesia does not cause significant maternal hypotension on mobilising once the spinal injection is given.
177	Peek 1995	Therapeutic trial	21	-16 normotensive women -5 women with pre-eclampsia (diastolic BP >100, proteinuria), on medication & for preterm delivery	SpaceLabs 90207 used to monitor BP before, during and after administration of thyrotropin releasing hormone (TRH) to promote fetal lung maturation.	Rises in systolic BP and mean arterial pressure were significantly greater in pre-eclamptic women after TRH vs normotensive women. BP levels of up to 190/135 were recorded.	In women with pre-eclampsia, TRH for fetal lung maturation should be used with great caution.
175	Neri 1999	Therapeutic trial	36	All women had BP>140/90 twice 4 hrs apart. 4 had proteinuria >0.3 g/24h.All >24 wks gestation	SpaceLabs 90207 ABPM at start & 2 wks after oral nifedipine (n=12), glyceryltrinitrate continuous (n=12) or intermittently (n=12).	30 women completed the study. No significant effects were seen on blood pressure in any groups using chronobiology methods.	ABPM effective and reliable method to evaluate effect of different treatment options

As discussed above, identification of women with white coat hypertension (WCH) using ABPM could potentially identify high risk groups more reliably and target intervention more appropriately. This is an area where ABPM is frequently used in the non-pregnant population. This phenomenon of persistently elevated clinic pressure with normal blood pressure at other times was first noted by Ayman and Goldshine over 60 years ago.[178, 30]

White coat hypertension is defined as the transient rise of a patient's BP in response to the clinic surroundings or the presence of the observer. In an early report Mancia measured intra-arterial blood pressure continuously while a doctor took regular blood pressure measurements using a cuff.[179] The extent of the rise in BP was surprisingly marked: in 'almost all' of the 48 normotensive and hypertensive subjects tested 'the doctor's arrival at the bedside induced immediate rises in systolic and diastolic blood pressures peaking within 1 to 4 minutes (mean 26.7 +/- 2.3 mm Hg and 14.9 +/- 1.6 mm Hg above pre-visit values).' By the end of the visit, levels had decreased to only slightly higher than the pre-visit readings.

Over the years the definition of WCH has been refined, and is now described as BP ≥140/90 mmHg in the office, with a normal daytime ABPM of <135/85, although the exact cut-off for ABPM varies slightly in the literature.[103, 180] WCH is found in 15-30% of the general population and should be considered in newly diagnosed hypertensives, although the lack of clinical characteristics makes this difficult. There is debate about whether this is a truly benign condition, and there is probably a small increase in risk compared to the normotensive population. It may precede development of 'true' hypertension. White coat hypertension is more common in female, young populations and therefore might be expected to arise in pregnancy. [37, 181]

Relevant studies of white coat hypertension in pregnancy are outlined in Table 1.9. Rayburn et al found that on ABPM, daytime systolic and diastolic BP were at least 5 mmHg lower than elevated clinic readings in 80% and 83% of women respectively.[182] They warned against unnecessary treatment of hypertension, suggesting a period of 'close observation' before making any therapeutic decisions in pregnant patients with WCH. In 1997 Biswas et al also found high rates of WCH at 28-37 weeks gestation, with only 38% of women diagnosed with 'non-proteinuric hypertension' in the clinic being truly hypertensive on ABPM using mean DBP of 85 mmHg as the threshold.[183] A mean 'white coat effect' on the systolic BP of 20 mmHg in normotensive women and 11 mmHg in hypertensive patients was noted. The authors suggest that in asymptomatic women with no proteinuria and clinic diastolic readings of 90-110 mmHg, the incidence of true hypertension is only 33% and justifies ABPM.

A series of papers from one group provide insight into the growing body of evidence on white coat hypertension in pregnancy. In 1999 Brown et al's paper 'The white coat effect in hypertensive pregnancy: much ado about nothing?' examined the presence of white coat hypertension (raised conventional BP and normal ABPM) and white coat effect (magnitude of difference between conventional BP and ABPM).[184] They found that systolic and diastolic WCH were present in only 3.2% and 4.2% of a group of 120 women in the second half of pregnancy with conventional BP of $\geq$ 140 mmHg systolic and/or $\geq$ 90 mmHg diastolic BP. They did however report a diastolic white coat effect of $\geq$ 10 mmHg in 20% of women in the study. Outcomes in this group (severe hypertension, anti-hypertensive drugs, abnormal laboratory values, birth weight and fetal growth restriction) were the same as women not exhibiting the effect. Possible explanations for the lower rate of WCH in this study include the inclusion of women with mild hypertension, screening before inclusion with averaging of

several conventional readings, and including women on anti-hypertensive drugs. However, the authors concluded that: 'we can see little point in recommending ABPM or other automated blood pressure devices for the purpose of identifying a white coat effect in women with hypertension in the second half of pregnancy.'

In a review of the subject in 2000, 'White coat hypertension in pregnancy: fact or fantasy?' Brown and Davis suggest two potential implications of white coat effect/hypertension in pregnancy.[185] The first is the administration of anti-hypertensive medication to pregnant women who may not have true hypertension. The second is the implication for prognosis of the pregnancy: is this finding benign or a marker for future complications? They suggest separate approaches to women in early and late pregnancy. The criteria for diagnosing raised BP on initial consultation are very important: studies suggest that repeated readings by a midwife rather than a doctor may lower rate of white coat hypertension (reflecting findings in non-pregnant patients). Supporting evidence includes a study by Turnbull et al which found increased rates of hypertension (10%) in women randomized to shared care as opposed to those with midwifery led care (4.8%), despite both groups of over 600 women being at equal risk.[186] In a study of day assessment unit care, 60% of women referred with raised BP in antenatal clinic had normal BP after a more prolonged period of readings by midwives.[187]

Olofsson and Persson also found, in women with mean gestation of 35 weeks, that the rate of WCH was nearly 30% following an initial raised BP[188], and Biswas diagnosed it in 62% of women.[183] However, in their own study in later pregnancy, Brown et al found a much lower rate of white coat hypertension (quoted above) after repeated readings by a midwife.[184] In summary, in later pregnancy midwifery recording of BP and repeating of elevated readings

on a day unit might decrease white coat effect and allow identification of a high-risk group, as in some studies outlined in Table 1.9 and discussed above. In at least one third of cases in women with no other worrying features the women will be normotensive and can be followed up on the day assessment unit.

However, in early pregnancy the situation is different. When BP is taken in young women, sometimes for the first time in their lives, a certain percentage will have white coat hypertension. Some women already carrying the label of 'essential hypertension' will also come into this group. Before long-term medication is started ABPM can help confirm true hypertension, and ongoing studies were suggested to confirm the risks in this group. In a later paper, Brown et al went on to recommend that the gold standard for diagnosis of WCH is ABPM, and that an automated self-initiated device showed wide limits of agreement and could not replace ABPM.[189]

Finally, in 2005 Brown's group reported on 'The natural history of white coat hypertension during pregnancy.' [190] In a cohort of 241 women with an early pregnancy diagnosis of essential hypertension, 32% had white coat hypertension on ABPM. Cut-off points for normal ABPM were ≤ 130/80 mm Hg at under 26 weeks and ≤ 135/85 mmHg after 26 weeks gestation.[191] In 50% the diagnosis of WCH was unchanged through pregnancy and no anti-hypertensives were given; for 40% of the women the diagnosis changed to gestational hypertension. Pregnancy outcomes were good for both these groups. Only 8% of these women developed pre-eclampsia, compared to 22% of the women with true essential hypertension (p=0.008). However, as in the study by Bellomo,[167] the caesarean section rate was high (40%) in the WCH group, possibly as a reaction to raised conventional BP

measurements near term. This emphasises uncertainties amongst clinicians in decision-making in these women.

Based on these findings, the paper recommended ABPM (or a validated home BP device) to establish if an initial diagnosis of essential hypertension in early pregnancy is correct. If white coat hypertension is found, outcomes should be much better but frequent monitoring is still necessary. This study repeated ABPM about every four weeks. By avoiding anti-hypertensive medication in women who have WCH thoughout pregnancy, about one in three women with apparent essential hypertension can avoid these drugs.

A large study in 2006 by Giannubilo et al described in Table 1.7, confirmed the role of ABPM in 223 pregnant women with mild chronic hypertension.[87] Superimposed pre-eclampsia developed in 34.9% and was predicted with a specificity of 89% using mean diastolic BP of 78 mmHg at 24 weeks gestation.

Table 1.9. Studies of ABPM values compared to conventional BP values, including white coat hypertension

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
182	Rayburn 1993	Prospective comparative	30	Previously normotensive women (mean gestation 31 wks) attending a routine clinic, latest office BP elevated to >140/90 or rise of 30/15 over booking BP.	SpaceLabs 90207 ABPM at home. Mean day and night values compared to office values taken with mercury, random zero sphygmomanometer.	In 27 women (90%), ABPM was below office values. In 3 women the levels were the same. In no case were ABPM values greater than office measurements.	This form of 'mild hypertension' in pregnancy is often specific to a clinic visit and may lead to unnecessary treatment.
192	Brown 1993	Prospective comparative	42	Pregnant women in third trimester: normotensive and hypertensive (numbers not given for each group)	Accutracker II ABPM Hawkesley random zero sphygmomanometer readings compared over 90 minutes seated (n=42) & 30 minutes standing/ walking (subgroup, n=20)	Seated and ambulatory ABPM overestimated systolic BP by 5 and 7 mmHg, & underestimated phase V diastolic BP by 3 & 4 mmHg respectively.	ABPM readings with the Accutracker II are reasonably comparable to mercury readings in pregnant women, particularly for group data.

Table 1.9. (cont.) Studies of ABPM values compared to conventional BP values, including white coat hypertension

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
188	Olofsson 1995	Prospective comparative	99	Pregnant women, mean gestation 35 wks, hospitalised for new hypertension (BP ≥140/90 at 2 consecutive visits & repeatedly raised thereafter).	SpaceLabs 90202 ABPM twice (n=14), 3 times (n=3) & 4 times (n=2), and routine conventional BP (CBP) in parallel at least 5 times daily. Note women hospitalised and on bed rest during monitoring.	ABPM SBP was significantly higher and DBP was significantly lower than CBP.	ABPM and CBP gave significantly correlated but different values of BP. New definitions of hypertension are needed if ABPM used in pregnancy.
193	Churchill 1996	Prospective comparative	239	-209 nulliparous pregnant women with no history of hypertension -30 nulliparous non pregnant women as controls	SpaceLabs 90207 ABPM at 18, 28, &36 wks gestation compared to random zero device. 62 cases had ABPM 12 wks postpartum .	24-hr median ABPM was higher than office BP in pregnancy ($p<0.001$). After delivery the difference was non-significant and was similar to other surveys and the non pregnant controls.	ABPM and CBP are different in pregnancy, and are different entities. Care should be taken in predicting obstetric outcome from the results of ambulatory BP recordings.

Table 1.9. (cont.) Studies of ABPM values compared to conventional BP values, including white coat hypertension

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
183	Biswas 1997	Prospective observational	128	Pregnant women 28-37 wks gestation with diastolic BP ≥90 mmHg twice 30 mins apart, and no proteinuria	SpaceLabs 90207ABPM at home.	Valid recordings in 120 women. 46 (38.3%) had true hypertension defined by ABPM (threshold 24-hr mean diastolic BP 85 mmHg.) White coat effect was seen in both groups, as mean BP was almost always lower than initial clinic readings.	White coat hypertension (WCH) is 'common' in pregnancy. ABPM can help identify true hypertension without requiring hospitalisation. 33.3% of asymptomatic patients with diastolic BP 90-110 mmHg have true hypertension.
194	Yohay 1997	Prospective observational	47	Pregnant women in the third trimester -17 pre-eclampsia: (BP ≥140/90 or >30/15 increase twice 6 hours apart.) -15 with chronic hypertension (BP as above <20 wks.) -15 normotensive	Accutracker ABPM. Note definition of pre-eclampsia does not include proteinuria.	ABPM readings were lower than CBP in hypertensive women. The difference was more pronounced in pre-eclamptic women than chronic hypertensives.	ABPM appears to be a promising method for the evaluation of hypertensive disorders of pregnancy.

Table 1.9. (cont.) Studies of ABPM values compared to conventional BP (CBP) values, including white coat hypertension (WCH)

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
191	Brown 1998	Prospective comparative	259	Attendees at routine antenatal or high risk for pre-eclampsia due to history. Women with chronic or white coat hypertension were excluded.	SpaceLabs 90207 ABPM up to four times in pregnancy. 276 successful studies made. Seven readings taken of alternating ABPM x3 & mercury readings x4. Smallest difference used to compare devices	Awake ABPM measurements are significantly higher than mercury device measurements. Only 2% of women discontinued monitoring. Normal ranges are described across gestation.	Women tolerate ABPM well and use is feasible in pregnancy. In a research setting with repeated readings in a relaxed setting, conventional values are lower than ABPM for 'awake' measurements.
195	Koenen 1998	Prospective cross-sectional comparative	10	Hospitalised pregnant women. Four had pregnancy-induced hypertension (diastolic BP >90).	SpaceLabs 90207 ABPM with repeated mercury measurements using Y-tube connector at 9 predetermined timepoints.	None of the contrasts between any pair of time points reached statistical significance. However, substantial within-subject variability of the pressure difference was seen.	Difficulty in estimating precisely the pressure difference between methods is an impediment for interpretation of ABPM data.

Table 1.9. (cont.) Studies of ABPM values compared to conventional BP values, including white coat hypertension

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
184	Brown 1999	Prospective blinded	121	Hypertensive women in second half of pregnancy admitted to hospital or antenatal day unit. Mercury readings done 4-6 times and averaged.	SpaceLabs 90207 ABPM WCH defined: mean mercury BP≥140 /90 & awake ABPM normal for gestation. White coat effect (WCE) is difference between them. Perinatal outcomes compared in women with and without WCE ≥20 (systolic) and 10 mmHg (diastolic).	Systolic and diastolic white coat hypertension in 3.2% and 4.2% of group. White coat effect found in 4.2% (systolic) & 20.2% (diastolic). Outcomes assessed in latter group (n=24) showed no difference compared to those without diastolic white coat effect.	White coat hypertension (WCH) is an 'infrequent occurrence' in mild late hypertension, no difference in outcome if present. Using ABPM to detect white coat effect in women with hypertension in the second half of pregnancy does not appear to be clinically useful.
196	Hermida 2004		403	-235 normotensive -128 gestational hypertension (>20 wks, BP>140/90 & raised hyperbaric index) -40 pre-eclampsia (BP as above & proteinuria >0.3g/ 24 h.)	SpaceLabs 90207 for 48 hrs from recruitment at <16 wks and 4-weekly. The tolerance-hyperbaric test (where diagnosis of hypertension is based on the hyperbaric index calculated by reference to a time-specified tolerance limit), is used.	When measured in the third trimester, hyperbaric index gave a sensitivity of 99.2% & specificity of 100% in predicting any pregnancy hypertension. This compares to 14.4% and 99.5% for systolic of 140 and 4% and 100% for diastolic BP.	Sensitivity of ABPM is superior to conventional BP in predicting hypertension when the hyperbaric index is used.

Table 1.9. (cont.) Studies of ABPM values compared to conventional BP values, including white coat hypertension

Reference	First author Year	Study design	Sample size	Subjects	Description	Findings	Conclusion
189	Brown 2004	Prospective observational	66	Pregnant women being assessed for possible 'white coat hypertension.', mean gestation 23 weeks.	SpaceLabs 90207 awake ABPM vs 6 self-initiated automated BP readings (Omron HEM 705CP). Primary outcome measure: Limits of agreement between BP on each device.	Average BP was identical (125/77) in both devices, but with wide limits of agreement (systolic -20 to +23 mmHg, diastolic -9 to +15 mmHg).	ABPM is the gold standard for clinical management of women with white coat hypertension. This Omron self-initiated device cannot reliably replace it as individual BP differences are probably too great.
190	Brown 2005	Prospective interventional	241	Pregnant women: early pregnancy diagnosis of essential hypertension (EH). 86 had the diagnosis confirmed pre-pregnancy as home monitor/ABPM≥ 135/85.	The remaining 155 women had SpaceLabs 90207 ABPM in early pregnancy. Those with white coat hypertension (WCH) were untreated & had ABPM monthly. Primary outcome: pre-eclampsia (spot urine:creatinine ≥ 30). 7 women excluded with miscarriage <20 weeks.	78/241 (32%) women had white coat hypertension. 38 (50%) retained this diagnosis and had good pregnancy outcomes as did the 32 (40%) with gestational hypertension. 6 (8%) developed pre-eclampsia vs 35 (22%) of women with essential hypertension (p=0.008).	About one third of women with apparent essential hypertension early in pregnancy have WCH. ABPM is recommended for diagnosis & ongoing surveillance, & should reduce use of antihypertensives by 1/3. Pregnancy outcomes are good in WCH.

The literature search revealed publications stating guidelines and recommendations on ABPM in pregnancy from specialist conferences, and position statements of various organisations. None of these give details of the literature search used and they are generally presented as consensus statements and expert opinion. Two papers mention the hierarchy of evidence assessed. In their statement on behalf of the British Hypertension Society, O'Brien et al[180] grade the strength of evidence according to Shekelle et al (Table 1.10)[197], allocating Grade C-D to recommendations on use of ABPM in pregnancy. McGrath[102] ,on behalf of the National BP Advisory Committee of the National Heart Foundation of Australia, provided overall recommendations graded according to the National Health and Medical Research Council quality-of-evidence ratings.[198] However, the recommendations related to ABPM use in pregnancy are not graded in this publication. Table 1.11 summarises these guidelines and statements.

Table 1.10 Classification schemes for interpreting evidence for guidelines[197]

Category of evidence	**Description**
Ia	Evidence for meta-analysis of randomised controlled trials
Ib	Evidence from at least one randomised controlled trial
IIa	Evidence from at least one controlled study without randomisation
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
Strength of recommendation	**Description**
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

Table 1.11. Guidelines and Society recommendations for ABPM in pregnancy

Reference Author Year	Group represented	Objective	Conclusions related to pregnant women	Recommendations
199 Staessen 1995	4th International Consensus Conference on ABPM (Leuven, Belgium, 1994)	Focus on technical aspects of ABPM in all patient groups	If monitor is used in special populations, a specific demonstration of its accuracy in these defined subgroups is warranted.	Validation of devices in pregnant women is essential.
200 Staessen 1999	7th International Consensus Conference on ABPM (Leuven, Belgium, 1999)	To reach a consensus on the clinical use of ABPM	-As with non-pregnant women, main indication for ABPM in pregnancy is to measure white coat effect, avoiding unnecessary /excess antihypertensive drugs. -Normal values have been defined -Evidence for prediction of pre-eclampsia inconclusive, but has predicted birth weight.	ABPM is 'especially indicated' for pregnant women.
180 O'Brien 2000	British Hypertension Society	To advise on the use and interpretation of ABPM in adults	-Main use in pregnancy is identifying white coat hypertension -Normal values are now defined through pregnancy -Correlates better with proteinuria and predicts complications of hypertension, including low birth weight, better than conventional BP -Women identified as white coat hypertensives have more Caesareans than normotensive women.	-ABPM may be used to avoid unnecessary hospital admission or drug administration. -Some caesarean deliveries might be avoided by identifying women with white coat hypertension. Overall conclusion: ABPM is of benefit in diagnosing and treating hypertension in pregnancy (evidence strength C–D, see text for details).

Table 1.11. (cont.) Guidelines and Society recommendations for ABPM in pregnancy

Reference Author Year	Group represented	Objective	Conclusions related to pregnant women	Recommendations
201 Staessen 2001	8th International Consensus Conference on ABPM (Sendai, Japan, 2001)	To reach a consensus on the prognostic significance of new techniques of automated blood pressure measurement.	Several studies of 'gestational hypertension' have shown that, compared to office measurement, ABPM is a better predictor of maternal and fetal complications.	-Pregnancy is a special indication for ABPM to measure the white coat effect and reduce unnecessary antihypertensive drug use. -Further studies are needed to address application of ABPM in high-risk pregnant women with chronic hypertension, Type 1 diabetes or hypertensive nephropathy.
102 McGrath 2002	National BP Advisory Committee of the National Heart Foundation of Australia: position statement.	To provide guidance on how and when ABPM should be applied in practice, and how to interpret results. NB hierarchy of evidence described but not applied to pregnancy recommendations.	ABPM should be considered in hypertension in pregnancy.	-ABPM has a role in assessing hypertension in pregnancy. -Definitive outcome studies are needed in the form of randomised controlled trials comparing management of hypertension based on office BP measurement vs ABPM (general recommendation for all patient groups.)

Further papers providing reviews, clinical overviews and commentaries on the use of ABPM in pregnancy are listed in Table 1.12. The QUORUM statement on assessment of quality of reporting of systematic reviews was used as a basis to assess the publications.[202] However, only one publication qualifying as a systematic review using formal meta-analysis was identified: a Cochrane review by Bergel and Carroli.[203] The title, structured abstract, and methodology for searching, selection, and validity assessment complied with the QUORUM checklist. There was a discussion with a future research agenda as suggested. As no randomized trials were identified for the meta-analysis, further QUORUM assessment on areas such as data abstraction and quantitative data synthesis was not relevant.

The other references described in Table 1.12 have been described as clinical overviews or commentaries to emphasise that they are not systematic reviews. Their main conclusions and recommendations are summarised in the table. Validation of the monitors used in pregnancy is frequently recommended in these publications. The need for objective validation of ambulatory monitors has been referred to in the discussion on ABPM in the general population (Section 1.4.1). Validation in pregnant women has been reviewed in Section 1.4.2 above.

Table 1.12. Reviews, overviews and commentaries on ABPM in pregnancy

Reference Author Year	Type of publication	Details (using QUORUM)	Findings / Conclusions	Recommendations
204 Halligan 1991	Clinical overview	Systematic review: No Structured abstract: No Literature search described: No Types of studies specified: No	-Five studies are underway in the use of ABPM in pregnancy. -Results so far indicate ABPM is an acceptable method of measuring BP in pregnancy.	Possible roles for ABPM in antenatal management of hypertension include modification of classification systems, clinical confirmation, and predicting pre-eclampsia
129 Greer 1993	Commentary	Systematic review: No Structured abstract: No Literature search described: No Types of studies specified: No	-Summarises three studies in that issue of the journal. -Concludes that ABPM can provide accurate assessment of blood pressure in pregnancy	-Consider Korotkoff V for measuring with ABPM. -If ABPM is used, it is important to relate these measurements to clinical outcome
30 Halligan 1995	Clinical overview	Systematic review: No Structured abstract: No Literature search described: No Types of studies specified: No	-Discusses device validation evidence, values in normal pregnancy, patient acceptability, use in preeclampsia, applications in antenatal care.	Overall, ABPM may lead to reappraisal of clinical management of hypertension in pregnancy. Potential uses include: -overcoming sampling, measurement and white coat hypertension errors of conventional BP -diurnal changes may aid diagnosis of pre eclampsia -cost and patient satisfaction benefits of outpatient monitoring

Table 1.12. (cont.) Reviews, overviews and commentaries on ABPM in pregnancy

Reference Author Year	Type of publication	Details (using QUORUM)	Findings / Conclusions	Recommendations
31 Halligan 1996	Clinical overview	Systematic review: No Structured abstract: No Literature search described: No Types of studies specified: No	-Discusses technical aspects including problems with conventional BP, validation of devices, reference values, and white coat hypertension in pregnancy. -ABPM has been introduced into clinical obstetric practice without evidence of significant benefit.	-May reduce number of antenatal admissions and direct clinical action to high-risk patients. -A randomised controlled trial is needed comparing ABPM to conventional BP measurement.
32 Walker 1998	CME review article	Systematic review: No Structured abstract: No Literature search described: No Types of studies specified: No	-Summarises limitations of conventional BP measurement, history and device validation in ABPM, patterns in normal pregnancy, ABPM and perinatal outcome.	-In pregnancy ABPM may be considered the optimal research instrument -The ultimate place of ABPM 'awaits clarification.'
6 Shennan 1998	Clinical overview	Systematic review: No Structured abstract: No Literature search described: No Types of studies specified: No	-Reviews significance of hypertension in pregnancy, limitations of conventional BP, equipment validation, use in pregnancy	-ABPM clearly has advantages over conventional measurement, with potential in assessing at risk hypertensive pregnancies. -Not always accurate especially in pre-eclampsia -Validate devices.

Table 1.12. (cont.) Reviews, overviews and commentaries on ABPM in pregnancy

Reference Author Year	Type of publication	Details (using QUORUM)	Findings / Conclusions	Recommendations
103 Pickering 2000	Clinical overview	Systematic review: No Structured abstract: No Literature search described: No Types of studies specified: No	One section of paper is on ABPM in pregnancy. It describes a study finding 29% of women with clinic hypertension have white coat hypertension; these women may have unnecessary caesarean sections. Reference not given for this paper.	No specific recommendations for ABPM in pregnancy.
205 Waugh 2000	Clinical overview	Systematic review: No Structured abstract: No Literature search described: No Types of studies specified: No	Discusses technical aspects including haemodynamic changes in normal and hypertensive pregnancy, and validation issues.	-Validation procedure is essential and should include formal validation in pre-eclampsia -Additional care must be taken in interpreting readings form devices not validated in pre-eclampsia.
33 Feldman 2001	Clinical overview	Systematic review: No Structured abstract: No Literature search described: No Types of studies specified: No	Summarises studies on patterns of ABPM in normal pregnancy and as a predictor of outcome in two tables. These describe study characteristics (how many subjects, trimester of monitoring, primary outcome) but do not formally assess quality or how studies selected.	-ABPM is promising in predicting pre-eclampsia in chronic hypertensive women. -Further research is needed to better define the role of ABPM in routine and high-risk obstetric practice.

Table 1.12. (cont.) Reviews, overviews and commentaries on ABPM in pregnancy

Reference Author Year	Type of publication	Details (using QUORUM)	Findings / Conclusions	Recommendations
206 Redon 2001	Clinical overview	Systematic review: No Structured abstract: No Literature search described: No Types of studies specified: No	Discusses reference values, prediction of pre-eclampsia and white coat hypertension.	-ABPM may be useful in 'gestational hypertension' -The role of ABPM in high-risk pregnancies needs to be explored.
37 Higgins 2001	Clinical overview	Systematic review: No Structured abstract: No Literature search described: No Types of studies specified: No	Discusses conventional and ABPM measurement in pregnancy, including white coat hypertension and prognostic value in late pregnancy.	-Careful blood pressure measurement with a mercury device remains the gold standard -All ABPM devices should be validated for use in pregnancy, preferably in patients with pre-eclampsia -Randomized trials of ABPM compared with conventional BP measurement in hypertensive women are now urgently needed
203 Bergel 2002	Systematic review for the Cochrane Library	Systematic review: Yes Structured abstract: Yes Literature search described: Yes Types of studies specified: Yes	Two reviewers evaluated all potentially relevant articles, examined each study for inclusion and assessed methodological quality using Cochrane guidelines. No trials were included.	-There is no randomized controlled trial evidence to support the use of ABPM during pregnancy. -Randomized trials are needed.

Table 1.12. (cont.) Reviews, overviews and commentaries on ABPM in pregnancy

Reference Author Year	Type of publication	Details (using QUORUM)	Findings / Conclusions	Recommendations
207 O'Brien 2003	Clinical overview	Systematic review: No Structured abstract: No Literature search described: No Types of studies specified: No	-Main use in pregnancy is identifying white coat hypertension -Normal values are now defined through pregnancy -Correlates better with proteinuria and predicts complications of hypertension, including low birth weight, better than conventional BP -Women identified as white coat hypertensives have more Caesareans than normotensive women.	-White coat hypertension may occur in ≤30% of pregnancies, main use of ABPM is to detect this. -Caesarean sections may be avoided if ABPM was used to measure BP rather than conventional technique.

Outpatient monitoring has potential benefits in cost and convenience to patients and institutions. The increasing use of ABPM in pregnancy coincided with the establishment of the obstetric day-care unit,[208, 209] with a trend away from prolonged antenatal admission for pregnancy complications such as hypertension. In the non-pregnant population there is now evidence that the additional costs of ABPM are offset in the first year by savings in patients with white coat hypertension (26% of the total) who would have otherwise received treatment.[210] These savings applied with the factoring in of a 10% conversion rate to established hypertension in those patients in whom WCH is a pre-hypertensive state. A related editorial suggested that the recognition of white coat hypertension in pregnancy 'has the potential to reduce anxiety, hospital admissions and drug use, with significant cost savings.' [211]

All relevant studies found in the literature search are listed in the tables above. The search was performed with the help of a clinical librarian, and a wide range of terms was used including truncated terms and alternative spellings. When full references were obtained their reference list was checked against the database for further publications. Every publication found relating in any way to the use of ABPM in pregnant women was included in the Tables. The reasons for not including studies, such as being automated rather than ambulatory monitoring, have been described in section 1.1.2. We did not actively seek unpublished studies and that could lead to missing studies and publication bias. The search excluded publications in languages other than English due to costs of obtaining full text papers and translating them. This is a potential disadvantage, which might lead to missing relevant papers.[212] However, our finding that there were no randomized trials of ABPM in pregnancy was the same as that of the published Cochrane review, conducted with the full support of the Cochrane Collaboration with no language restrictions.

There were limitations in many of the publications described in the tables above, with small numbers of patients (few had power calculations), giving a higher chance of a Type II error (false negative). They often did not include information on potential confounding variables for outcomes such as age, parity, or ethnicity. It could not be defined whether they were prospective or retrospective studies in some cases and there was a lack of reporting of patients excluded from analysis; this could lead to selection bias. As discussed in section 1.3.1, the problem of the varied definitions of hypertension in pregnancy was evident in reviewing the publications; when definitions were given they are included in the tables above.

Within those limitations, the research described above suggests that there are valid reasons for believing that ABPM assessment of hypertensive pregnant women may be superior to conventional antenatal clinic blood pressure readings in two main ways. Firstly, it will identify women suffering from white coat hypertension and thereby prevent unnecessary treatment and monitoring. Secondly, by assessing the blood pressure more accurately obstetricians will be able to identify women at risk of adverse perinatal outcomes. These two aspects are not mutually exclusive: it is likely that the correct identification of women with white coat hypertension allows better allocation of risk.

However, all the studies performed so far are cohort or case controlled studies and thus subject to bias. They may not have identified adverse consequences of ABPM, such as more and possibly unnecessary obstetric intervention. Alternatively, the beneficial effects of ambulatory blood pressure monitoring may have been considerably over-estimated. The clinical effectiveness of ABPM needs to be tested in a prospective randomized study, comparing the technique with conventional methods of monitoring blood pressure in

pregnant women. A paper published in the Lancet in 2001 stated that such randomized trials are now urgently needed.[37]

The Cochrane review (latest view date December 2007) entitled 'Ambulatory versus conventional methods for monitoring blood pressure during pregnancy', stated that: 'given the observational data suggesting that ABPM can enhance assessment of blood pressure in pregnancy, and experimental data in non-pregnant subjects showing that hypertensive patients monitored with ABPM might have better outcomes, there is a clear need for randomized trials of ABPM compared with conventional blood-pressure measurement in pregnancy, and in particular in hypertensive pregnant women. There is no randomized controlled trial evidence to support the use of ABPM during pregnancy.' [203]

1.5 AIMS AND OBJECTIVES OF THIS THESIS

This thesis aims to test the hypothesis that in pregnancies complicated by hypertension, ambulatory blood pressure monitoring improves clinical assessment and outcome for both mother and fetus. There are three objectives:

-To quantify the risks of hypertension in pregnancy to mother and baby in a local multi-ethnic population.

-To ascertain the extent to which the technique of ambulatory blood pressure monitoring (ABPM) is useful in the assessment of hypertensive pregnancies, and assess its predictive value for significant maternal and fetal outcomes.

-To evaluate the potential benefits of employing ABPM in hypertensive pregnancies in the clinical setting.

These objectives will be met by conducting the following experiments/investigations:

-Analysis of a local database of 625 pregnancies in women with hypertension, specifically assessing maternal and fetal outcomes in different diagnostic and ethnic groups.

-A retrospective analysis of ABPM in a cohort of 100 hypertensive pregnant women, to determine the specific maternal and fetal predictive qualities of the technique.

-A randomized controlled trial of ABPM in hypertensive pregnancies in the clinical setting. Hypertensive pregnant women not requiring delivery within 24 hours were eligible. All had 24-hour ABPM as well as conventional BP measurement. Half of the participants had the monitoring results revealed to the clinician, and the other half had their results concealed. Primary outcome measures were admission to hospital for hypertension, antihypertensive medication, induction of labour for hypertension, and caesarean section.

CHAPTER 2:

PERINATAL OUTCOMES IN A MULTI-ETHNIC HYPERTENSIVE, PREGNANT POPULATION

2.1 ABSTRACT

Objective: To investigate obstetric, perinatal and neonatal outcomes in hypertensive women attending a specialist antenatal clinic.

Design: Retrospective cohort study

Setting: An inner city hospital antenatal hypertension clinic.

Participants: 627 pregnancies in 509 women with prospective data from 1980-2002.

Main outcome measures: Obstetric, perinatal and neonatal outcomes

Results: From a database of 627 pregnancies, 317 (50.6%) had chronic hypertension (CH), 123 (19.6%) gestational hypertension (GH), 61 (9.7%) secondary hypertension (SH) and 45 (7.2%) pre-eclampsia (PE). Compared to the obstetric population, pregnancies in hypertensive women had an increased risk of Caesarean section, and (with the exception of GH) a baby weighing <2.5 kg or delivered preterm. Overall in the study population, there were increased rates of stillbirth in pregnancies in Black (40:1000) and Asian (64.8:1000) compared to White women (14:1000), though statistical significance was only reached comparing pregnancies in White and Asian women (percentage difference -5.1%; 95% confidence intervals (CI) -6.9, -1.5; p=0.007). Perinatal mortality rates (PMR) per 1000 live and stillbirths were lower in pregnancies in White vs Asian women: (28.0 vs 83.3, percentage difference -5.5%; 95% CI -8.4, -1.2; p=0.013). Outcomes in chronic hypertension were analysed further. Pregnancies with chronic hypertension alone had lower perinatal mortality rates than with superimposed pre-eclampsia (49.8 vs 115.9, percentage difference -6.6%; 95% CI -14.2, -0; p=0.049). Pregnancies in White women with chronic hypertension had lower stillbirth rates compared to Asian women: 11:1000 vs 102:1000 (percentage difference -9.1%; 95% CI -10.8, -2.6; p=0.008). The majority (88.2%) of stillborn babies from pregnancies in chronic hypertensive women weighed less than the 10^{th} centile.

Compared to White women, more pregnancies in Asian women with CH were booked after 20 weeks gestation (White vs Asian 3.2 % vs 18%, percentage difference -14.8%; 95% CI -18.8, -6.4; p=0.001). The mean birth weight was greater in pregnancies in White women compared to those in Asian women (2.73 vs 2.37 kg, difference 0.36 kg; 95% CI 0.12, 0.6; p=0.003). 51% of pregnancies in Asian women and 43.9% of those in Black women delivered a baby under 2.5 kg vs 31.2 % of White women (p=0.016 overall).

Conclusion: This cohort seen in one centre with complete follow-up is comparable with other series in the world literature. Our results confirm the high perinatal mortality rates in pregnancies in women with chronic hypertension. Black and Asian chronic hypertensive pregnancies are particularly at risk due to increased rates of stillbirths of low birth weight babies.

2.2 INTRODUCTION

The hypertensive disorders of pregnancy and their important implications for feto-maternal outcome have been described in Section 1.3. A detailed and prospectively gathered computerised database is held for women attending a specialist antenatal hypertension clinic at City Hospital, Birmingham. Women want accurate information about the likely outcome of their pregnancy, particularly if they have a pre-existing medical condition such as chronic hypertension. Clinicians also need to be able to accurately allocate risk factors for adverse outcomes, and indeed the whole principle of antenatal care is underpinned by risk assessment. This study was conducted to address these issues for a local population and also for pregnant women in general.

Previous analysis of 436 pregnancies from the database reported increased risks of perinatal mortality, preterm delivery and lower birth weight in Indo-Asian women with chronic essential hypertension.[213] A further database study of pre-eclampsia and other obstetric outcomes in pregnancies of 159 normotensive and 213 chronic hypertensive women was published in 2001.[84] Further analysis of obstetric and neonatal outcomes in 627 pregnancies in women attending this antenatal hypertension clinic, including 317 chronic hypertensive pregnancies, is reported below. Outcomes in pregnancies in the different diagnostic groups and amongst different ethnic groups were of particular interest.

2.3 METHODS

All women attended the antenatal hypertension clinic at a District General Hospital in Birmingham. The hospital serves a population of about 300,000 people, of whom 64% are White, 25% are Indo-Asian and 11% are Afro-Caribbean. Ethnicity was self-reported, using

the hospital definitions in use at the time of the data collection. Information on demographic data, clinic blood pressure (BP) measurements, blood tests, drugs, complications and obstetric and neonatal outcomes are recorded prospectively onto a proforma. Seemingly spurious or extreme values are checked with the hospital notes. The data are then entered into a computerised database and validated. Two further researchers checked the data by cross-checking the proforma against the database manually for each entry. Outlying data or obvious errors were re-checked with the original hospital notes. For the current study, active follow-up of babies was conducted to ascertain their status at one week of age, to obtain accurate data for early neonatal deaths, and thus the true perinatal mortality rate.

Pregnant women are referred to the clinic by their midwife, general practitioner or obstetrician early in the pregnancy because of a history of pre-eclampsia or hypertension in a previous pregnancy, known chronic hypertension, or the discovery of hypertension in the first trimester. A team comprising of an obstetrician and physician with an interest in hypertension then conducts all pregnancy care. The BP is measured according to a strict protocol. The woman is seated in a quiet room with her right arm supported and the correct-sized cuff sited at the level of the heart. The first and fifth Korotkoff sounds are taken for systolic and diastolic BP respectively and a total of three readings taken over a minimum of three minutes.[214] The recorded blood pressure is the average of the last two readings. Initially the Hawksley Random Zero sphygmomanometer was used, to reduce observer error. Over the last five years, the Omron HEM 705 CP automatic blood pressure measuring device was used. All devices are regularly calibrated and their accuracy checked. Proteinuria is measured using dipstick urine testing (Multistix, Bayer, USA) and where applicable, by 24-hour urine collection for total protein.

A cohort of pregnancies in women from the database were analysed retrospectively. Obstetric and neonatal outcomes in 627 pregnancies in 509 women attending the clinic between 1980 and 2002 were studied. Hypertensive disorders were classified by criteria described by Davey and McGillivray[53] and endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) (Table 2.1). Renal hypertension was defined as hypertension in the presence of renal disease diagnosed pre-pregnancy, or when history and investigations confirmed renal disease. The final diagnosis was made in retrospect when two researchers independently classified the cases. If there was any disparity the cases were discussed and agreement reached. Data used in the analysis included maternal age, ethnicity, smoking status, parity, medication at booking, blood pressure, gestation at delivery, mode of delivery and birth weight. Birthweight centiles were classified as per the Child Growth Foundation Charts.[215] Stillbirth was diagnosed in babies born at or after 24 weeks gestation with no signs of life. Perinatal mortality rate was defined as the total number of stillbirths and early neonatal deaths (those occurring in the first week of life) per 1000 live and stillbirths.

Continuous variables are expressed as mean (range), mean (standard deviation) or medians (interquartile range), and categorical variables as percentages. The Anderson-Darling normality test was used to test for normal distribution of continuous variables. Statistical tests performed were the χ^2 test, Fisher's exact test and analysis of variance (ANOVA). A p value of 0.05 was considered significant. The Bonferroni correction was used for multiple comparisons, dividing 0.05 by the number of comparisons to obtain a p value. Data were analysed using Excel, statpages.org online calculators and Minitab version 13.1 [216].

Table 2.1. Definitions of hypertensive disorders in pregnancy

Hypertension in pregnancy

A. Diastolic blood pressure of ≥110 mmHg

B. Diastolic blood pressure of ≥90 mmHg on two or more occasions >4 h apart

Proteinuria in pregnancy

A. One 24-hr urine collection with total protein excretion ≥300 mg

B. Two clean midstream urine samples collected >4 h apart with 1+ on reagent strip with specific gravity <1030 and pH <8

Pre-eclampsia

Hypertension plus proteinuria in a previously normotensive woman

Gestational hypertension

Hypertension after the 20th week of pregnancy in a woman not known to have previous chronic hypertension, resolving after 6 weeks post delivery.

Chronic hypertension

Hypertension at the first booking visit before the 20th week of pregnancy in the absence of trophoblastic disease, or at any stage of pregnancy in a woman known to have chronic hypertension, or at more than 6 weeks after delivery.

Chronic hypertension with superimposed pre-eclampsia

Chronic hypertension with proteinuria developing towards the end of pregnancy

2.4 RESULTS

Diagnostic categories for the pregnancies in the study are shown in Table 2.2 below. Using the definitions in Table 2.1, pregnancies were assigned to diagnostic groups as shown. On assessment in the clinic, in 45 pregnancies hypertension was not confirmed by strict criteria. 22 were diabetic pregnancies and 5 multiple pregnancies. These were not included in the hypertensive diagnostic groups due to these confounding factors. Six pregnancies ending with first trimester miscarriage and three with no outcome data were found, and these were also not placed in the hypertensive groups, as outcomes could not be analysed.

Table 2.2 Diagnosis in 627 pregnancies in 509 women

Diagnosis	**No of pregnancies: n (%)**
Chronic hypertension	317 (50.6)
-No pre-eclampsia	248/317 (78.2)
-Superimposed pre-eclampsia	69/317 (21.8)
Gestational hypertension	123 (19.6)
Secondary hypertension	61 (9.7)
-Renal	53/61 (86.9)
-Other	8/61 (13.1)
Pre-eclampsia	45 (7.2)
Other: not assigned to hypertensive diagnostic groups	81 (12.9)
-Normotensive	45
-Diabetes	22
-Multiple pregnancy	5
-Miscarriage <12 weeks	6
-No outcome data	3

Maternal characteristics, mode of delivery, gestation at delivery and birth weight are shown in Tables 2.3 and 2.4. Information is included for the entire clinic study population of 627 pregnancies in the first column of these tables, followed by pregnancies in the different diagnostic groups, and the hospital obstetric population as a whole in 1994 (where data were available from the Hospital Annual Report). In Table 2.3, as expected, mothers in pregnancies with chronic hypertension tended to be older, with a median age of 32 years. There was also a trend for a higher proportion of chronic hypertensive pregnancies to be in women of Black ethnic origin (38.8% vs 28.5% of the clinic population). Overall, 27% of the clinic study population were pregnancies in primiparous women: this was higher in the pregnancies with pre-eclampsia where 37.8% were in primiparous women.

In Table 2.4, pregnancies in all diagnostic groups had a significantly higher risk of caesarean delivery compared to the general obstetric population rate of 16.6% ($p<0.013$). All pregnancies in hypertensive diagnostic groups (except gestational hypertensives) were more likely to deliver before 37 weeks, compared to the general obstetric population. With the exception of gestational hypertensive pregnancies, there was also an increased risk of delivering a low birth-weight baby (<2.5 kg).

Table 2.3. Maternal characteristics in pregnancies in total study population & different diagnostic groups.

	Total study population n=627	**Chronic hypertension** n=317	**Gestational hypertension** n=123	**Secondary hypertension** n=61	**Pre-eclampsia** n=45
Age (years):					
-median (IQR)	31 (26-35)	32 (28-36)	29 (24-33)	27 (24-32)	30 (26-33)
-NK	1	0	0	0	0
Ethnicity: n (%)					
-Asian	225 (35.9)	100 (31.5)	49 (39.8)	227 (44.3)	21 (46.7)
-Caucasian	220 (35.1)	93 (29.3)	55 (44.7)	26 (42.6)	15 (33.3)
-Black	179 (28.5)	123 (38.8)	18 (14.6)	8 (13.1)	9 (20)
-Other	1 (0.2)	1 (0.3)	0	0	0
-NK	2 (0.3)	0	1 (0.8)	0	0
Primiparous:					
-n (%)	169 (27)	68 (21.5)	44 (35.8)	19 (31.1)	17 (37.8)
-NK	1 (0.2)	0	0	0	0

See Table 2.2 for details of exclusion criteria for allocation to diagnostic group.

IQR = interquartile range

NK = not known

Table 2.4. Obstetric and neonatal data

	Total study population n=627	**Chronic hypertension** n=317	**Gestational hypertension** n=123	**Secondary hypertension** n=61	**Pre-eclampsia** n=45	**Hospital 1994*** n=3664	**Statistically significant results† Hypertensive diagnostic groups vs hospital obstetric population.* % difference (95% confidence intervals)**
Mode of delivery: n (%)							
-Normal	300 (47.8)	152 (47.9)	65 (52.8)	23 (37.7)	15 (33.3)		
-Instrumental	43 (6.9)	23 (7.3)	12 (9.8)	2 (3.3)	2 (4.4)		
-Elective caesarean	120 (19.1)	57 (18.0)	25 (20.3)	20 (32.8)	7 (15.6)	241 (6.6)	
-Emergency caesarean	141 (22.5)	77 (24.3)	21 (17.1)	15 (24.6)	20 (44.4)	267 (10.0)	
-Total caesarean	261 (41.6)	134 (42.3)[a]	46 (37.4)[b]	35 (57.4)[c]	27 (60)[d]	608 (16.6)	a 25.7% (20.3, 31.2) b 20.8% (12.7, 29.6) c 40.8% (28.3, 52.4) d 43.4% (28.8, 56.4)
-Other/NK	23 (3.7)	8 (2.5) ‡	0	1 (1.6)	1 (2.2)		

Table 2.2 has exclusion criteria for allocation to diagnostic group.

* Hospital data from Annual Report † χ^2 test, $p<0.013$, Bonferroni correction for multiple comparisons ‡ 7 mid-trimester losses, 1 not recorded

Table 2.4. (cont.) Obstetric and neonatal data

	Total study population n=627	**Chronic hypertension** n=317	**Gestational hypertension** n=123	**Secondary hypertension** n=61	**Pre-eclampsia** n=45	**Hospital 1994*** n=3664	**Statistically significant results† Hypertensive diagnostic groups vs hospital obstetric population.* % difference (95% confidence intervals)**
Gestation (wks): -median (IQR) -NK: n (%)	 38 (35-39) 6 (1)	 38 (34-39) 1 (0.3)	 38 (37-39) 0	 37 (34-39) 0	 35 (32-37) 0		
Gestation <37 wks: -n (%)	205 (32.7)	116 (36.6)[a]	16 (13)	29 (47.5)[b]	26 (57.8)[c]	442 (12.2)	a 24.5% (19.4, 29.9) b 35.5% (23.5, 47.8) c 45.7% (31.3, 59.0)
Birth weight (kg): -median (IQR) -NK: n (%)	 2.8 (2.1-3.3) 30 (4.8)	 2.6 (1.9-3.2) 7 (2.2)	 3.0 (2.6-3.5) 2 (1.6)	 2.8 (1.8-3.2) 4 (6.6)	 2.3 (2.6-2.8) 1 (2.2)		
Birth weight <2.5 kg: -n (%)	217 (34.6)	134 (42.3)[a]	27 (22)	24 (39.3)[b]	26 (57.8)[c]	507 (13.6)	a 28.4% (23.1, 33.9) b 25.5% (14.2, 38.0) c 43.9% (29.5, 57.2)

IQR=interquartile range. 5 twin pregnancies excluded in birth weight data in 1st column 'Total'. Table 2.2 has exclusion criteria for allocation to diagnostic group.

* Hospital data from Annual Report † χ^2 test, $p<0.013$, Bonferroni correction for multiple comparisons

Perinatal outcomes are shown in Table 2.5. The first row shows initial analysis of outcomes in all 605 singleton pregnancies of 24 weeks or over in the entire clinic population where ethnic origin and outcomes were available. There were increased rates of stillbirth in pregnancies in Black and Asian women, which were statistically significant (p=0.007) when comparing pregnancies in White and Asian women (percentage difference -5.1%; 95% confidence intervals -6.9, -1.5). Perinatal mortality was also significantly worse (p=0.013) in pregnancies in Asian compared to White women (White vs Asian percentage difference -5.5%; 95% confidence intervals -8.4, -1.2).

The data were then analysed separately for pregnancies in women in the different hypertensive diagnostic groups to compare perinatal outcomes. In pregnancies in women with chronic hypertension, superimposed pre-eclampsia conferred a significantly increased risk of perinatal death, giving a perinatal mortality rate of 115.9:1000 in this group (Table 2.5).

Table 2.5. Perinatal outcomes

	All births ≥24 weeks	**Stillbirths n (%)**	**Statistical analysis**	**Early neonatal deaths**	**Perinatal mortality n (%)**	**Statistical analysis**	**Stillbirth rate****	**Perinatal mortality rate****
All pregnancies in clinic:*	605	24 (4.0)		8	32 (5.3)		39.7	52.9
Ethnic group:								
-White women	214	3 (1.4)[a]	a vs b: p=0.007†	3	6 (2.8)[c]	c vs d: p=0.013†	14.0	28.0
-Black women	175	7 (4.0)	% difference (95% CI):	1	8 (4.6)	% difference (95% CI):	40.0	45.7
-Asian women	216	14 (6.5)[b]	-5.1% (-6.9, -1.5)	4	18 (8.3)[d]	-5.5% (-8.4, -1.2)	64.8	83.3
Diagnostic groups:								
-Gestational hypertension	123	3 (2.4)		2	5 (4.1)		24.4	40.7
-Secondary hypertension	60	1 (1.7)		4	5 (8.3)		16.7	83.3
-Pre-eclampsia (PE)	45	2 (4.4)		0	2 (4.4)		44.4	44.4
-Chronic hypertension:								
-Uncomplicated	241	11 (4.6)		1	12 (5.0)[e]	e vs f: p=0.049‡	45.6	49.8
-Superimposed PE	69	7 (10.1)		1	8 (11.6)[f]	% difference (95% CI): -6.6% (-14.2, -0)	101.4	115.9
-Total	310	18 (5.8)		2	20 (6.5)		58.1	64.5
West Midlands 1994							6.1	10.6

* Excludes pregnancies in women with unknown outcomes/ethnic origin, ethnic origin 'other' & multiple pregnancies. CI = confidence interval

Significant p values shown: χ^2 and Fisher's exact tests. † χ^2 test: p<0.017 Bonferroni correction for multiple comparisons ‡ χ^2 test: p <0.05.

** Stillbirth & perinatal mortality rates per 1000 total births ≥24 weeks gestation.

West Midlands data: Confidential Enquiry on Stillbirths and Deaths in Infancy (CESDI) 4th Annual Report[217]

As shown in Table 2.5, most stillbirths in the pregnancies in the hypertensive diagnostic groups (18 out of 24) occurred in the mothers with chronic hypertension. These 18 cases were examined further. Two women had two stillbirths each, and two women underwent obstetric hysterectomy for postpartum haemorrhage. No babies had congenital anomalies, and all presented as antepartum intrauterine deaths. Further characteristics of the pregnancies and babies where stillbirth occurred are shown in Table 2.6. The majority of babies were small, with 88.2% having birth weights below the 10^{th} and 58.8% below the 3^{rd} centile. Pregnancies in Black and Asian women with chronic hypertension had higher rates of stillbirth compared to White women, statistically significant for pregnancies in White vs Asian women (percentage difference -9.1%; 95% confidence intervals -10.8, -2.6; p=0.008).

Table 2.6. Details of stillbirths in 18 of 317 chronic hypertensive pregnancies

	Births ≥24 weeks*	**Number of stillbirths n (%)**	**Stillbirth rate per 1000 births ≥ 24 weeks**
Ethnic origin -White -Black -Asian	 90 121 98	 1(1.1)[a] 7 (5.8) 10 (10.2)[b] a vs b: p=0.008† % difference (95% CI): -9.1% (-10.8, -2.6)	 11 58 102
	Findings		
Superimposed pre-eclampsia: -White -Black -Asian	 1 / 1 4 / 7 2 / 10		
Gestation (weeks): -mean (range) -median (IQR)	 28.3 (24-38) 27 (25-31)		
Birth weight (kg) ‡ -mean (range) -median (IQR)	 0.92 (0.36-3.1) 0.60 (0.52-1.09)		
Birth weight <2.5 kg‡	16/17 (94.1%)		
Birth weight <10th centile	15/17 (88.2%)		
Birth weight <3rd centile	10/17 (58.8%)		

* One pregnancy in woman ethnic origin 'other'; seven pregnancies mid-trimester loss <24 weeks

† χ^2 test. Only p values significant at p<0.017 shown (Bonferroni correction)

CI=confidence intervals

‡ Birth weight not recorded in one case. Birth weight centiles adjusted for sex and gestation.

To examine potential confounding factors that might explain the variation in stillbirth rates in different ethnic groups, all 317 pregnancies in the Black, White and Asian women with chronic hypertension were compared in Table 2.7 (one pregnancy in a woman with ethnic

group ‘other’ was excluded). There were no differences in age. Pregnancies in White women were more likely to be defined as primiparous compared with Asian and Black women. Rates of smoking were assessed and pregnancies in White women had the highest rates of smoking (23.7%). However, up to 13% of pregnancies had missing data and numbers were relatively small (only 1% of pregnancies in Asian women were in smokers) so statistical analysis to compare groups could not be done. Data on body mass index were also not collected.

More pregnancies in Black women were conceived on anti-hypertensive drugs compared to pregnancies in White women, although this did not reach statistical significance: 46.3% vs 33.3%, p=0.054. Levels of blood pressure at three stages of pregnancy were also compared to see if severity of hypertension varied between the three ethnic groups. The mean diastolic BP at over 30 weeks gestation was the only statistically significant different measurement and was higher in pregnancies in White women.

Of note is that data are unavailable on BP readings under 20 weeks gestation due to late booking in 3 (3.2%) pregnancies in White women, 11 (8.9%) in Black women and 18 (18%) in Asian women. Pregnancies in Asian women were found to be significantly more likely to be booked for antenatal care after 20 weeks compared to those in White women (White vs Asian percentage difference -14.8%, 95% confidence intervals -18.8, -6.4). Rates of superimposed pre-eclampsia and preterm delivery were similar in the three groups. The mean birth weight was greater in pregnancies in White women compared to those in Asian women (2.73 vs 2.37 kg, difference 0.36 kg; 95% confidence intervals 0.12, 0.6; p=0.003). Over half the pregnancies in Asian women and 43.9% of those in Black women with chronic hypertension resulted in babies with birth weights under 2.5 kg, significantly more than the rate in pregnancies in White women (statistics in Table 2.7, p=0.016 overall).

Table 2.7. Characteristics of 316 pregnancies with chronic hypertension by ethnicity

	White (n=93)	**Black (n=123)**	**Asian (n=100)**	**Test**	**P value**	**% difference (95% confidence intervals) For significant results**
Age (years): mean (SD)	31.4 (5.4)	32 (5.9)	31.9 (5.7)	ANOVA	0.793	
Primiparous: n (%)	30 (32.2)[a]	26 (21.1)[b]	11 (11)[c]	χ^2 test	0.001 overall	a vs b 11.1% (-0.7, 22.5) a vs c 21.3% (9.9, 30.2) b vs c 10.1% (0.3, 18)
Smoker: n (%) NK	22 (23.7) 8 (8.6)	11 (8.9) 16 (13.0)	1 (1.0) 1 (1.0)	-	-	
Anti-hypertensive drug at conception: n (%)	31 (33.3)[a]	57 (46.3)[b]	34 (34)	χ^2 test	0.078 overall 0.054 a vs b	
Mean systolic BP (mmHg): -<20 wks gestation: mean (SD) NK: n (%) -20-30 wks gestation: mean (SD) NK: n (%) >30 wks gestation: mean (SD) NK: n (%)	 136.7 (15.0) 3 (3.2)[a] 134.0 (10.6) 6 (6.5) 139.0 (11.6) 11 (11.8)	 136.3 (15.6) 11 (8.9) 135.3 (15.2) 5 (4.1) 137.7 (17.3) 14 (11.4)	 134.9 (13.5) 18 (18)[c] 135 (14.5) 4 (4) 138.1 (15.6) 13 (13)	 ANOVA χ^2test ANOVA ANOVA	 0.716 0.001 a vs c 0.774 0.836	 a vs c -14.8% (-18.8, -6.4)

NK=not known. ANOVA=Analysis of variance BP levels may be unknown as patient not yet booked in clinic or delivered preterm

Table 2.7. (cont.) Characteristics of 316 pregnancies with chronic hypertension by ethnicity

	White (n=93)	**Black (n=123)**	**Asian (n=100)**	**Test**	**P value**	**% difference or difference between means (95% confidence intervals) For significant results**
Mean diastolic BP (mmHg): mean (SD)*						
<20 wks gestation	86.9 (9.9)	84.7 (9.6)	86.8 (10.0)	ANOVA	0.203	
20-30 wks gestation	84.3 (7.7)	83.1 (11.2)	85.7 (9.3)	ANOVA	0.143	
>30 wks gestation	90.2 (7.3)[a]	86.2 (11.0)[b]	89.2 (9.5)[c]	ANOVA	0.009 overall	a vs b 4.0 mmHg (1.25, 6.75) a vs c 1.0 mmHg (-1.57, 3.57) b vs c -3.0 mmHg (-5.92, -0.08)
Superimposed pre-eclampsia: n (%)	20 (21.5)	30 (24.4)	19 (19)	χ^2test	0.623	
Gestation at delivery (wks): mean (SD)	36.5 (4.9)	36.2 (4.5)	35.4 (4.7)	ANOVA	0.235	
Gestation at delivery <37 wks: n (%)	30 (32.3)	42 (34.1)	44 (44) [NK:1]	χ^2test	0.159	
Birth weight (kg): mean (SD)	2.73 (0.82)[a] [NK: 3]	2.49 (0.93)[b]	2.37 (0.84)[c] [NK:4]	ANOVA	0.017 overall, a vs c 0.003	a vs b 0.24 kg (0, 0.48) a vs c 0.36 kg (0.12, 0.6) b vs c 0.12 kg (-0.12, 0.36)
Birth weight <2.5 kg: n(%)	29 (32.2)[a] [NK: 3]	54 (43.9)[b]	51 (53.1)[c] [NK:4]	χ^2test	0.016 overall	a vs b -11.7% (-24.1, 1.6) a vs c -20.9% (-34.1, -6.7) b vs c -9.2% (-22.2, 4.1)

NK=not known. * Data for values NK as systolic BP in first section of table above. ANOVA=Analysis of variance

BP levels may be unknown as patient not yet booked in clinic or delivered preterm

Another possible confounder when assessing perinatal outcomes relates to the fact that the database spans a long time period (1980-2002.) Obstetric practice has changed over this time. The high overall stillbirth rates in pregnancies complicated by chronic hypertension might be related to different practices in the early years of data collection. Table 2.8 shows the distribution over time of chronic hypertensive pregnancies, divided into periods of five years (last time period three years.) These are divided by ethnic group and show trends of stillbirth over time. Four cases with missing data on year of birth (including one mid-trimester loss), one case of ethnicity 'other' and 6 further cases of mid-trimester loss are excluded from stillbirth data. Statistical analysis is not done as the absolute numbers are low, but the trends can be seen. The Caesarean section rate over these time periods for the same cases is also shown.

The highest stillbirth rate of 100 (per 1000 births ≥24 weeks) is seen in the earliest time period (1980-84). However, following this the rate fluctuates, with the lowest rates of 33:1000 and 28:1000 followed by two periods with higher rates. On analysing the Caesarean section rate, the lowest rate in 1980-84 (38%), is followed by an overall increase in rates with some variation.

Table 2.8. Stillbirths and caesarean section rates in pregnancies with chronic hypertension by time period.*

Years (total no of pregnancies)*	Chronic hypertensive pregnancies ≥ 24 weeks (n)			No. of stillbirths (n)			Stillbirth rate:1000 births ≥ 24 weeks	Caesarean section n (%)
	White	Black	Asian	White	Black	Asian		
1980-84 (n=40)	12	11	17	0	1	3	100	15 (38)
1985-89 (n=61)	6	24	31	0	0	2	33	28 (46)
1990-94 (n=71)	24	29	18	0	1	1	28	28 (39)
1995-99 (n=76)	23	36	17	1	3	2	79	35 (46)
2000-02 (n=58)	23	21	14	0	2	2	69	28 (48)
1980-2002 (n=306)	**88**	**121**	**97**	**1**	**7**	**10**	**59**	**134 (44)**

*Excludes 11 pregnancies in total: 4 pregnancies with missing data on year of birth (includes 1 mid-trimester loss), 6 further mid-trimester losses and one pregnancy in woman ethnic origin ‘other’.

2.5 DISCUSSION

This study represents one of the largest British series in the literature of pregnancies in hypertensive women undergoing antenatal care in a single centre. Data were collected prospectively and neonates followed up to seven days of age. The pregnancies in women with chronic and secondary hypertension represent the proportion of pregnant women in our population with these disorders, as strenuous efforts are made to identify them and refer them to the specialist antenatal hypertension clinic. The statistics for perinatal outcome in these women are based on accurate denominator data, as all pregnancies in women with these diagnoses in our population will be included.

However, for pregnancies complicated by pre-eclampsia and gestational hypertension, the entire populations of pregnancies in women with those diagnoses are not represented, and denominator data are incomplete. Pregnancies in women seen in the clinic with these disorders may represent a subgroup with atypical or serious disease, and this may explain the high perinatal mortality rates in these groups when compared to other papers, particularly in pregnancies in women with gestational hypertension.[44, 63, 66] There may be a bias towards an increased proportion of pregnancies in women with early-onset pre-eclampsia, and caution should be exercised when interpreting results from a small group of pregnancies with isolated pre-eclampsia who attended the clinic.

We analysed data by pregnancy rather than individual woman attending the clinic. Some women had more than one pregnancy. Overall, 627 pregnancies were assessed in 509 women. The outcomes we were reviewing, particularly perinatal outcomes, use the individual pregnancy as the denominator. It would not be possible for example to assess

gestation, Caesarean section rates or stillbirth by woman rather than by pregnancy. Each pregnancy is assessed on it's own characteristics and outcomes as would happen in clinical practice. The group of 18 stillbirths analysed in pregnancies in women with chronic hypertension occurred in 16 women (two women had two stillbirths), so were not skewed by a small number of patients with poor obstetric history.

The incidence of chronic hypertension in pregnancy is set to rise with the trend for delayed child-bearing.[218] There has been some discussion in the literature about whether risks of poor outcome in pregnant women with chronic hypertension are confined to those with severe disease and those developing superimposed pre-eclampsia.[76, 81, 82] A systematic review by Ferrer et al examined 46 studies reporting risks of prematurity, small for gestational age, low birth weight and fetal growth restriction, and concluded that in all but two papers, chronic hypertension was associated with an increased risk of these outcomes.[219] Women with chronic hypertension in our study had significantly more low birth weight babies (42.3% vs 13.6%) compared to the hospital obstetric population (Table 2.4).

Most of the studies in Ferrer's review did not separate outcomes in mild and severe chronic hypertensives, precluding comparisons between the two groups. Women with high-risk chronic hypertension are also reported to be at risk of serious maternal complications including pulmonary oedema, hypertensive encephalopathy, stroke and renal failure, as well as preeclampsia and placental abruption.[220] Expert advice and consensus in a recent review suggests high-risk women (for example, with target organ damage, BP >180/110, and age over 40 years) should have aggressive antihypertensive therapy and monitoring.[218] The benefit of medication in uncertain in those of lower risk, who have better expected outcomes.

This review stated an urgent need to conduct randomized trials, especially needed as a meta-regression analysis has shown a link between anti-hypertensive treatment and restricted fetal growth.[221] With a view to conducting such a trial, a 2003 paper studying 305 patients found 16.4% of pregnancies achieved the primary outcome of one or more serious perinatal complications/birth weight < 3rd centile in women with non-proteinuric hypertension at <34 weeks.[86] Interestingly, outcomes were the same for gestational and pre-existing hypertension. Subsequently, a pilot study of the ongoing CHIPS (control in hypertension in pregnancy study) trial with 132 women (same criteria) showed a definitive trial of outcomes in tight vs less tight BP control is feasible.[222] Non-proteinuric gestational hypertension (GH) has traditionally been associated with better outcomes, but recent work states that when severe, GH can result in more adverse perinatal outcomes than mild pre-eclampsia.[85, 223] Diagnostic allocation is not rigid: up to 50% of women with GH will progress to preeclampsia and some may have undiagnosed chronic hypertension. This is of interest in relation to the poor outcomes for women with gestational hypertension attending our clinic, alluded to above.

Preterm delivery was studied by Sibai et al in women with chronic hypertension (n=761) and normal pregnancies (n=2738).[83] Compared to women with uncomplicated pregnancies, those with chronic hypertension had more 'indicated' preterm deliveries (21.9% vs 3.4%), but the same rate of spontaneous preterm delivery. This suggests that rather than hypertension leading to preterm labour, it is intervention by the medical team that leads to early delivery of the baby. In our study, 36.6% of women with chronic hypertension delivered preterm compared to the overall hospital rate of 16.5% Chronic hypertensives also had more caesarean sections: 42.3% vs 16.6% (Table 2.4, $p<0.013$), suggesting babies born preterm were due to early elective delivery.

In their systematic review Ferrer et al concluded that chronic hypertension consistently tripled the risk for perinatal mortality with an odds ratio of 3.4 (95% CI 3.0-3.7), compared to normotensive mothers or general obstetric populations.[219] The perinatal mortality rate of 49.8:1000 in our study was much higher than the general population, even in cases uncomplicated by pre-eclampsia. The extremely high perinatal mortality rates of 115.9:1000 in our series in women with chronic hypertension and superimposed pre-eclampsia have been reported previously in the literature. Sibai et al described perinatal death rates of 24% in 21 of 211 mild chronic hypertensives with superimposed pre-eclampsia,[69] and 32% in 91 women with chronic hypertension in 303 cases of severe pre-eclampsia.[70] In a further paper studying pregnancies in 44 women with severe chronic hypertension, 23 women developed superimposed pre-eclampsia with a perinatal mortality of 48%: all deaths in the series occurred in this group.[71] Mabie et al described the course of 169 pregnancies with chronic hypertension where women with superimposed pre-eclampsia necessitating delivery at 27-34 weeks gestation had a perinatal mortality of 238:1000.[72] In 1990 Ferrazzani et al reviewed 444 hypertensive women and found a perinatal mortality rate of 129:1000 in a group combining superimposed pre-eclampsia and pre-eclampsia.[74]

In a detailed analysis of 337 chronic hypertensive pregnancies Rey et al described an incidence of perinatal death of 10.8% with superimposed pre-eclampsia.[76] A New Zealand study found a perinatal mortality rate of 80:1000 in 26 women with superimposed pre-eclampsia.[81] Sibai et al's 1998 paper using strict diagnostic criteria in 193 women with superimposed pre-eclampsia reported a perinatal death rate of 8%.[82] In view of the poor associated perinatal outcomes with superimposed pre-eclampsia, it is important to establish the risk of developing this complication: in our study this was 21.8%. This is comparable

with rates in the literature of 10% [69], 17% [81], 21.4% [76], 25% [82], 28.4% [87], 34% [72] and 52% [71]. The large variety in rates may partly be due to variation in definitions used and populations studied, and are a good example of difficulty in comparing published data in this field. Using current definitions in 154 women with severe hypertension a 2004 study quoted rates of superimposed pre-eclampsia of 78%.[224]

The incidence of superimposed pre-eclampsia did not vary significantly between the three ethnic groups of women in our study (Table 2.7), although 38.8% of women with chronic hypertension were Black compared to 28.5% of the clinic population (Table 2.3). Some previous authors have described an increased risk of superimposed pre-eclampsia and other adverse outcomes in Black compared to White women with chronic hypertension. The established increased incidence of chronic hypertension in Black women was confirmed by Ananth et al with a relative risk of 1.9 when compared to White women in a paper analysing nearly 300,000 pregnancies in total.[78] In 1996 in the USA the incidence of chronic hypertension was 25.0:1000 deliveries among Black (African-American) women, an excess of 14.5 cases per 1000 deliveries compared with rates for other women.[225] Rey and Couturier describe a relative risk of 2.2 (95% CI 1.4-3.4) for superimposed pre-eclampsia in Black vs White chronic hypertensive women, confirmed by logistic regression analysis.[76] Samadi et al quote similar rates, with a doubling of the risk of superimposed pre-eclampsia in African-American vs White women with chronic hypertension.[226] In contrast, Sibai et al reported that black race was not a risk factor for superimposed pre-eclampsia in an analysis of 763 women with chronic hypertension.[82] In 2005, Bryant et al reported that Black women without chronic hypertension were also more likely to have pre-eclampsia than White women, and increased pre-eclampsia rates in this population could not be solely attributed to higher rates of chronic hypertension.[227]

Ananth et al describe an increased absolute risk of stillbirth in Black vs White chronic hypertensive women, although after adjustment for potential confounders such as age, education and smoking, adjusted risk ratios tended to be greater among Whites compared to Blacks (stillbirth was defined as occurring after 20 weeks gestation in this study).[79] A study specifically addressing comparisons between White and Black women found superimposed pre-eclampsia, perinatal mortality and prematurity to be significantly more frequent in Black than in White women with chronic hypertension.[88] Rates of perinatal mortality and prematurity were raised in Black chronic hypertensives without pre-eclampsia compared to Black normotensive pregnant women, but no such difference was found between White chronic hypertensive women without pre-eclampsia and their White normotensive control group. The authors suggest ethnic differences in perinatal outcomes in these women are not purely explained by superimposed pre-eclampsia.

The effect of ethnicity on maternal outcome in hypertension in pregnancy was assessed by Mackay et al in 2001, reviewing 4024 maternal mortalities.[60] Black women were 3.1 times more likely to die from pre-eclampsia or eclampsia as those of White ethnicity. Further work is needed to identify what differences contribute to this excess perinatal and maternal mortality and address it with specific interventions. The possibility that poor access to medical care and higher prevalence of chronic disease with generally poorer physical fitness may explain previously reported elevated risks of hypertension in pregnancy in Black women was explored in a 1994 paper studying 8259 pregnant women in the military.[228] The authors suggest that health, education and socio-economic differences between black and white populations are significantly reduced in this group: in particular there was equal access to health care. Their hypothesis was supported in that Black and White women in this selected population appeared to be at equal risk for the development of all pregnancy-

induced hypertension, but this paper excluded those with pre-existing chronic hypertension. Unfortunately no data on socio-economic status of women were collected in our study; therefore it was not possible to investigate the possible confounding effects of this variable.

Although a body of literature exists assessing differences in White and Black women in this field, there is little data about perinatal outcomes in hypertensive Asian women compared to those of other ethnic groups. In a 2007 study of 197,061 nulliparous women in London, perinatal mortality was highest among South Asian women at all gestational ages.[229] Among South Asian and Black women the most important factor linked with antepartum stillbirth was birth weight below 2000g; hypertension was not included in this logistic regression analysis. In our study, marked differences in perinatal mortality rates were found between pregnancies in women in the three ethnic groups. When pregnancy outcomes in all women attending the clinic were assessed, stillbirth was more common in pregnancies in Black and Asian women, and statistically more frequent in pregnancies in Asian compared to White women. Perinatal mortality was also significantly raised in pregnancies in Asian women when compared to those in White patients. This is consistent with previous database publications, with perinatal mortality quoted as 1.6% for White & 10% for Asian women.[213]

Previous work on this database also reports stillbirths in 4.47% of 179 pregnancies with uncomplicated chronic hypertension, and 5.9% of 34 pregnancies with superimposed pre-eclampsia.[84] With further data, our results for 317 chronic hypertensive pregnancies showed stillbirth rates of 45.6:1000 and 101.4:1000 respectively. Most stillbirths occurred in pregnancies in women with chronic hypertension. We examined pregnancy characteristics in this diagnostic group to assess possible factors contributing to the increased risk. We also examined the possibility of confounding factors, particularly in pregnancies in Black and

Asian women in this group when compared to White women, which might contribute to the increased risks in these ethnic groups. Documented characteristics of pregnancies at raised risk of stillbirth include extremes of maternal age, smoking, inequalities and social deprivation, obesity, prior stillbirth, and medical problems such as diabetes, hypertension and antiphospholipid antibodies. Congenital anomalies, fetal growth restriction & congenital infections are among recognised causes. However, many stillbirths are still classified as 'unexplained.' [230, 231]

When assessing the characteristics of pregnancies with chronic hypertension in our study group, more pregnancies in White women were primiparous. However, the mean age of the mothers in the three ethnic groups was not significantly different. There were no significant differences (with one exception) between the blood pressure measurements in the three groups. It is noted that there was a non-significant trend for more pregnancies in Black than White women to be booked with the mother on anti-hypertensive drugs, which might indicate more severe disease and mask potentially higher levels of BP in this group. Unfortunately rates of smoking and effect of body mass index could not be assessed due to small numbers and missing data. We did assess trends over time to see if figures were skewed by adverse outcomes from early years of the database, and found that although the highest rate of stillbirth was in the first five years, subsequent time periods showed a fluctuating rate with no definite pattern of declining rates.

Babies born to Black and Asian chronic hypertensive women were lighter than White babies. No significant link was found between ethnicity and anti-hypertensive treatment (Table 2.7) to explain these differences.[221] There are known racial differences in birth weight particularly in Asian babies, which may contribute to this effect.[232] When assessing the

stillborn babies, growth restriction was common in these pregnancies in women with chronic hypertension, with 88.2% of the babies having a birth weight less than the 10th centile corrected for sex and gestation. In summary, the raised perinatal mortality figures in pregnancies in Black and Asian women with chronic hypertension therefore generally represent mothers presenting with intrauterine deaths of growth-restricted babies with a mean gestational age of 28.3 weeks. Prematurity and low birth weight in surviving babies will contribute to morbidity but were of limited importance in perinatal mortality. None of the stillborn babies in this group had congenital anomalies.

The role of growth restriction in stillborn babies in the West Midlands has been highlighted in reports from the West Midlands Perinatal Institute (WMPI).[233] In 1997 to 2005, fetal growth restriction was the commonest feature of stillborn babies, present in over 40% of cases. Efforts need to be directed to encouraging women to attend early for antenatal care, and detecting the growth-restricted fetus. Customised growth charts allowing for effects of ethnicity, parity and body mass index are recommended by WMPI, aiding more accurate diagnosis and classification of small babies. The possible link between anti-hypertensive medication and growth restricted babies also needs further investigation.[221]

A West Midlands Perinatal Institute (WMPI) report on trends, factors and inequalities on stillbirths and infant mortality in the West Midlands from 1997-2005 was published in 2007.[233] The report used the Index of Multiple Deprivation (IMD) to assess five quintiles of increasing deprivation. This area based score, revised in 2007, contains seven domains which relate to income deprivation, employment deprivation, health deprivation and disability, education skills and training deprivation, barriers to housing and services, living environment deprivation, and crime.[234] For stillbirth and perinatal mortality rates, the report

showed the gap between most deprived and the rest of the population was shown to be increasing in recent years, with the highest rates in the populations living in the most deprived quintile.

The data on address which is needed to calculate deprivation scores such as the IMD were not in our database. It is possible that this is an important confounding factor, if Asian and Black women with pregnancies in the study were more likely to live in deprived areas than White women. The WMPI report above did show that overall, when compared to mothers of European-British origin, babies of African Caribbean, Pakistani and Indian mothers were at significantly increased risk of stillbirth, perinatal death and infant death. Whether confounded by social deprivation or not, this is a high risk group for adverse perinatal outcomes. These findings support the generalisability of our results.

We found that pregnancies in Asian women with chronic hypertension were more likely to be booked in clinic after 20 weeks gestation than White women, and this lack of early antenatal care may be relevant in this group. The WMPI report also showed rates of booking with the midwife within the first 12 weeks were lowest in Asian and Afro-Caribbean mothers. Late booking is a known marker for poor pregnancy outcome for mother and baby.[58]

In summary, our study supports current targeted measures in women to encourage earlier attendance in pregnancy, detect growth restricted babies and intervene appropriately, especially in pregnancies in women with chronic hypertension from Asian and Black ethnic groups, who have been found to be at increased risk of antepartum stillbirth in this study.

In its eighth annual report, the Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI), now the Confidential Enquiry into Maternal and Child Health (CEMACH) introduced an enquiry into the care of diabetic pregnancies, which was reported in 2007.[231, 235] CESDI stated that diabetes is the most common pre-existing medical disorder complicating pregnancy in the UK (4:1000 pregnancies) and quoted perinatal mortality rates of 36.1:1000 - 42.8:1000. The perinatal mortality rates we have quoted in this study for women with chronic hypertension exceed those for diabetic women, and when pre-eclampsia is superimposed on chronic hypertension, rates are nearly three times higher than for diabetes. Chronic hypertension occurs in 1-5% of pregnant women, a similar incidence to diabetes, and will be increasingly more common as the average age of childbearing continues to rise. Asian and Black women are particularly at risk. Hypertension in pregnancy, particularly chronic hypertension, would be a suitable area for a future CEMACH enquiry.

Review of our database has shown the burden of perinatal morbidity and mortality in women with hypertension in pregnancy. Improvements are needed in the process of allocating risk in pregnancy, with better prediction of adverse outcome and targeting of appropriate care. Section 1.4.3 of this thesis has reviewed the use of ambulatory blood pressure monitoring (ABPM) in pregnancy. In the next chapter an analysis of the predictive value of ABPM is presented.

CHAPTER 3:

A RETROSPECTIVE ANALYSIS OF THE USE AND PREDICTIVE VALUE OF AMBULATORY BLOOD PRESSURE MONITORING IN 100 PREGNANT HYPERTENSIVE WOMEN

3.1 ABSTRACT

Objective: To determine the accuracy with which ambulatory blood pressure monitoring (ABPM) can predict obstetric and neonatal outcomes.

Design: Retrospective records-based cohort study

Setting: Obstetric department of a district general hospital

Participants: 100 hypertensive pregnant women undergoing ABPM.

Main outcome measures: Regression analysis to assess correlation of conventional BP monitoring (CBPM) and ABPM with obstetric and perinatal outcomes

Results: Of 100 women, 18 had chronic hypertension, 50 needed antihypertensive drugs and 84 were admitted for hypertension; 36 had labour induced for hypertension and 57 had caesarean sections. Twenty-seven babies were preterm; 22 went to the neonatal unit. There was one 23-week fetal loss, one stillbirth and one neonatal death. Development of proteinuria, and gestation and weight at birth were significantly associated with mean ABPM systolic and diastolic pressures. These were more accurately predicted compared to CBPM.

Conclusion: ABPM predicted certain obstetric and neonatal outcomes more accurately than CBPM.

3.2 INTRODUCTION

Measurement of blood pressure is the most commonly used screening test in pregnancy. Hypertensive disease of pregnancy is consistently a leading cause of direct maternal mortality in the United Kingdom, with the mortality rate from pre-eclampsia and eclampsia unchanged over two of the last three Confidential Enquiries into Maternal Deaths, and a slight increase in the 2007 Report.[57, 58] Morbidity to both mother and fetus is significant, particularly when premature delivery is needed.[236]

Ambulatory blood pressure monitoring (ABPM) is established in management in the non-pregnant hypertensive individual and has been reviewed above in Section 1.4.

3.3 OBJECTIVES

ABPM in pregnancy had been used at our unit for eight years. We performed a detailed analysis of its use and assessed its predictive ability for important obstetric and neonatal outcomes in our clinical setting. The study was a pilot study preceding the randomized study reported in chapter four of this thesis.

3.4 METHODS

Subjects

One hundred pregnant hypertensive women underwent ABPM from 1996–2002, using the SpaceLabs ambulatory blood pressure monitor 90207.[115] The technique was performed as described in section 4.3 ‘Monitors and ambulatory monitoring process.’ All women had hypertension in pregnancy and had ABPM as requested by a consultant obstetrician.

Data collection

The medical notes were examined and data placed on a proforma (Appendix 2). These data were entered onto an Excel database and analysed using Excel and MiniTab version 13.1.[216] Birthweight centiles were classified as per the Child Growth Foundation Charts.[215] Conventional blood pressure readings were an average of the two most recent measurements taken at least 4 hours apart. Hypertensive disorders were classified as in Chapter 2, using the criteria described by Davey and McGillivray, endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) and shown in Table 2.1.[53]

Statistical analysis

Initial analysis of outcomes was performed using descriptive statistics. Results are given using median (interquartile range) or percentages. Single and multiple linear regression analyses were done for continuous outcomes. Logistic regression analysis was done for binary outcomes, with categorical variables entered as factors in the model. Significance was set at $p < 0.05$. Odds ratios and 95% confidence intervals are given for binary outcomes.

3.5 RESULTS

The women had a median age of 31 (interquartile range 26-35) years with a body mass index (BMI) of 27.4 (23-33) kg/m^2; 58% were nulliparous. Ninety-five % were White, with 4% Asian and 1% Black. Only 6% were current smokers. One or more medical problems were present at booking in 38%, with 18% of the total noted to have chronic hypertension. Overall, 6% were on anti-hypertensive drugs at booking. Of those with previous pregnancies, 36% had pre-eclampsia and 38% had been delivered by caesarean section.

The women had a median of 6 (3-12) days in hospital antenatally and 11 (7-17) inpatient days in total. Overall, 84% were admitted for hypertension a median of 2 (1-2) times.

Clinical pregnancy data are shown in Table 3.1. There were three perinatal losses: a miscarriage at 23+3 weeks gestation, an intrauterine death at 40+2 weeks, and early neonatal death at 24+3 weeks. The diagnosis at discharge was pre-eclampsia in 34%, chronic hypertension in 23%, and pre-eclampsia superimposed on chronic hypertension in 10%. At discharge, 43% of the women were taking anti-hypertensive drugs.

All women had ABPM: 80% had one episode, 12% two, 7% three and 1% four episodes. Results are in Table 3.2. Regression analysis was done to assess the correlation between conventional and ambulatory blood pressure readings and significant pregnancy outcomes. This is shown in Table 3.3. Predictors included in all models were age, BMI and consultant. Numbers of smokers and non-white race were too small for inclusion. For growth restriction and birth weight, the model also includes primiparous status and previous baby weighing <2.5 kg. For gestation at delivery and preterm delivery, the model also includes previous baby <37 weeks gestation. For proteinuria of 2+ or more on dipstick testing, the model also includes primiparous status. For day unit attendance, the outcome is corrected for gestation at delivery. For caesarean delivery, the model also includes previous Caesarean section

Table 3.1. Pregnancy data and obstetric/neonatal outcomes (n=100)

	Yes	**No**	**Not done**
24-hour urinary protein >0.3g	24%	22%	54%
Proteinuria ≥2+ on dipstick	32%		
Antenatal steroids	17%		
Antenatal anti-hypertensive drugs	49%		
Acute anti-hypertensive drugs	16%		
Induction of labour	53%		
	Hypertension	Post-term	Other
Indication for induction	36 (68%)	8 (15%)	9 (17%)

	Normal	Elective CS	Emerg CS	Ventouse
Mode of delivery	39%	15%	42%	4%

HDU admission	13%
Magnesium sulphate given	4%
Gestation at delivery (weeks)*	38.6 (36.9-40)
Delivery <37 weeks gestation	27%
Birth weight (g)*	3082 (2611-3461)
Birth weight <10th centile	19%
Male infant	53%
Female infant	47%
Neonatal unit (NNU) admission	22%
Length of stay on NNU (days)*	17 (5-38)
Length of stay all babies*	5 (3-6)

*Median (interquartile range)

Table 3.2. ABPM results

	ABPM 1 (n=100)	**ABPM 2** (n=20)	**ABPM 3** (n=8)	**ABPM 4** (n=1)
Gestation (weeks)	29.7 (20.3-34.2)	28.7 (23.6-32.1)	32.2 (29.7-33.2)	31.1
Duration (hrs:min)	23:27 (22:44-23:55)	22:57 (11:17-23:33)	23:10 (10:49-23:53)	23:51
No. of readings	46 (40-48)	44 (26-46)	43 (31.8-47.5)	49
% successful	94 (90.8-97)	94 (92-97)	94 (90-96.3)	100
24-hour mean SBP	128 (122-136)	138 (126.5-145.3)	137 (126.8-146.8)	129
24-hour mean DBP	79 (74.8-86)	86 (79.8-92.3)	89.5 (79-94.3)	76
CSBP*	140 (130-148)	145 (137-150)	140 (138.5-142)	142
CDBP*	90 (84.8-98)	98 (90-101)	93.5 (85-103)	84

Results as median (interquartile range), mmHg unless stated otherwise.

*CS/DBP=conventional systolic/diastolic BP at time of ABPM

Table 3.3. Regression analysis of conventional vs. ambulatory blood pressure monitoring for perinatal outcomes

Outcome	**Conventional Systolic BP**		**Conventional Diastolic BP**		**24-hr mean Systolic BP**		**24-hr mean Diastolic BP**	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
IUGR <10thcentile p value Odds ratio (95% CI)	0.25 1.02 (0.98,1.06)	0.31 1.02 (0.98,1.06)	0.89 1.00 (0.95,1.06)	0.76 1.01 (0.95,1.07)	<0.01 1.08 (1.03,1.14)	<0.001 1.11 (1.05,1.18)	0.01 1.08 (1.02,1.15)	<0.01 1.11 (1.03,1.20)
Birth weight p value	0.03	0.03	<0.01	0.05	<0.001	<0.001	<0.001	<0.001
Birth weight <2.5 kg p value Odds ratio (95% CI)	0.04 1.04 (1.00,1.09)	0.06 1.04 (1.00,1.08)	0.05 1.05 (1.00,1.11)	0.14 1.04 (0.99,1.10)	<0.001 1.11 (1.05,1.17)	<0.001 1.12 (1.06,1.19)	<0.001 1.15 (1.07,1.24)	<0.001 1.16 (1.07,1.25)
Gestation at delivery p value	0.07	0.11	0.08	0.02	<0.001	<0.001	<0.001	<0.001
Delivery <37 weeks p value Odds ratio (95% CI)	<0.01 1.06 (1.02,1.11)	0.01 1.06 (1.01,1.10)	0.02 1.06 (1.01,1.12)	0.02 1.07 (1.01,1.13)	<0.001 1.09 (1.04,1.15)	<0.001 1.11 (1.05,1.17)	0.001 1.10 (1.04,1.17)	<0.001 1.14 (1.06,1.23)
Proteinuria p value Odds ratio (95% CI)	0.11 1.03 (0.99,1.06)	0.13 1.03 (0.99,1.06)	0.09 1.04 (0.99,1.09)	0.13 1.03 (0.99,1.06)	<0.01 1.07 (1.03,1.12)	<0.01 1.07 (1.03,1.12)	0.01 1.07 (1.02,1.13)	<0.01 1.08 (1.02,1.15)
Day unit attendance p value	0.97	0.94	0.37	0.27	0.05	0.02	0.15	0.08
Caesarean section p value Odds ratio (95% CI)	0.03 1.04 (1.00,1.08)	0.06 1.04 (1.00,1.08)	0.04 1.05 (1.00,1.09)	0.02 1.06 (1.01,1.12)	0.01 1.05 (1.01,1.09)	0.02 1.06 (1.01,1.11)	0.06 1.05 (1.00,1.10)	0.02 1.08 (1.01,1.15)
Admission to HDU p value Odds ratio 95% CI	0.02 1.07 (1.01,1.21)	0.02 1.06 (1.01,1.12)	0.05 1.06 (1.00,1.13)	0.06 1.06 (1.00,1.14)	<0.01 1.10 (1.04,1.17)	<0.01 1.11 (1.04,1.18)	<0.01 1.14 (1.05,1.23)	<0.01 1.16 (1.06,1.27)

3.6 DISCUSSION.

The technique of ABPM has been used in our unit for several years, as it has in obstetric units throughout the country. However, there have been no formal randomized prospective trials of its use to date in the literature. This study confirmed that ABPM can be performed reliably in a district hospital using midwives on the antenatal day unit, who are familiar with the technique. Good compliance was achieved, with median duration of recording over 22 hours long (Table 3.2).

This is a selected population from a specific geographical area, with 95% of White ethnicity, and only 6% were current smokers. Results should be applied to other populations with caution. Patients were referred by consultants for ABPM as part of routine practice in our unit. It is possible that individual variation in management affected outcomes such as gestation at delivery. Individual patient characteristics might also bias the results, for example women with a previous caesarean, small baby or preterm delivery would be more likely to have a repeat of this outcome. Individual risk factors such as body mass index or age might also affect results. For this reason these factors were built into the relevant models for regression analysis to allow for their confounding effect and to examine the relative predictive value of ambulatory versus conventional blood pressure monitoring.

ABPM results had better correlation with certain obstetric and neonatal outcomes compared with conventional blood pressure monitoring in this retrospective study. In particular, outcomes of birth weight less than the 10^{th} centile (corrected for sex and gestation), preterm delivery and significant proteinuria correlated better with 24-hour mean values. This suggests that a raised ABPM result could predict these adverse outcomes more accurately

than conventional methods, and thus identify women at higher risk. Previous studies described in Chapter 1, Table 1.7 have reported similar findings.

The benefit of ABPM may be from obtaining more reliable readings and identifying women with white coat hypertension, thus correctly identifying those with true hypertension in pregnancy. Using this method, a decrease in unnecessary interventions should result, without adverse effects on perinatal outcomes. ABPM may also be a more accurate predictor of outcome compared to conventional BP on its own merits, with the 24-hour period of readings during normal activity innately better linked to outcomes. These mechanisms may be inter-related, or act independently.

The results above are useful in confirming previous research findings. However, the true test of the technique is whether it is being used to maximum benefit in a clinical setting. In particular, the question arises of whether ABPM is a useful adjunct to clinical care of women with hypertension in pregnancy, or simply confirms the suspicion of disease without changing management strategies. Given the lack of assessment of ABPM in pregnancy in any prospective randomized controlled trials,[203] a Lancet review stated these are 'urgently needed.' [37] Following the above results, we conducted a prospective randomized trial of the use of ABPM in pregnancy.

CHAPTER 4:

A RANDOMIZED COMPARISON OF AMBULATORY BLOOD PRESSURE MONITORING VERSUS CONVENTIONAL OFFICE BLOOD PRESSURE MEASUREMENT IN THE MANAGEMENT OF PREGNANT HYPERTENSIVE WOMEN

4.1 ABSTRACT

Objective: To test the hypothesis that ABPM, by identifying pregnant women with white coat hypertension in pregnancy, would lead to a reduction in obstetric and neonatal interventions compared to conventional blood pressure measurement in a pragmatic clinical setting.

Design: Prospective randomized controlled trial.

Setting: Obstetric department of a district general hospital

Participants: 100 pregnant women undergoing ABPM with randomization to revealed or concealed results.

Main outcome measures: Obstetric and perinatal outcomes including admission to hospital, induction of labour, caesarean section, preterm delivery, use of anti-hypertensive drugs. All participants were sent a questionnaire after delivery about their experience of ABPM.

Results: The rate of induction for hypertension was 23% lower in the 'revealed' ABPM group when compared to the 'concealed' group ($p=0.015$). The overall rate of induction of labour was also lower in the 'revealed' compared to the 'concealed' group (37.3% vs 49%) but did not reach statistical significance ($p=0.236$). Other variables examined showed no statistically significant differences between groups. Of the women returning the questionnaire, 56/63 (89%) stated they would undergo ABPM in a future pregnancy.

Conclusion: This study showed a reduction in the rate of induction for hypertension when ABPM results were available. It does not show any other clinical benefit of ABPM in hypertensive pregnant women. The heterogeneous nature of the study population in this pragmatic trial may have affected these results. Better understanding is needed of which group of hypertensive pregnant women will benefit from ABPM. ABPM requires further robust evaluation in clinical practice. Patient acceptance of the procedure is high.

4.2 INTRODUCTION

Background

This thesis aims to test the hypothesis that in pregnancies complicated by hypertension, ambulatory blood pressure monitoring (ABPM) improves clinical assessment and outcome for both mother and fetus. The objective of this section is to evaluate the potential benefits of employing ABPM in hypertensive pregnancies in the clinical setting, by reporting the results of a randomized controlled trial. This is the first prospective randomized clinical trial of ABPM, as confirmed in a Cochrane Review which found no studies to report.[203] The use of ABPM in pregnant and non-pregnant subjects has been discussed in detail in section 1.4.

4.3 METHODS

Participants

Inclusion criteria

Any pregnant woman with a diagnosis of hypertension during pregnancy qualified for trial entry. Subjects were classified using the system devised by Davey and MacGillivray and endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP), Table 2.1.[53] For the purposes of the study, hypertension was defined as two diastolic readings at least 4 hours apart of ≥ 90 mmHg, using the fifth Korotkoff sound**.**

Exclusion criteria

1. Any woman whose conventional blood pressure measurement was so severely raised that it warranted immediate treatment with intravenous anti-hypertensives and delivery within the 24-hour assessment period.
2. Women with a concurrent medical condition such as diabetes or renal disease.
3. Women under the age of 16 or unable to give informed consent.
4. In the concealed results group, any women with an ABPM result defined as severe hypertension (170/110 or more) by recognized guidelines.[45] Clinicians would be notified of the results.

Participating centre

Good Hope Hospital NHS Trust, Sutton Coldfield participated in the trial, with all six consultants agreeing to enrol their patients. This district hospital in the West Midlands had a birth rate of 3200 deliveries per annum during the study period (2003). Originally a further centre was to participate, but this hospital withdrew from the study for logistical reasons.

Randomization and intervention

Before commencing the trial, several presentations were given to staff to publicise it. One-to-one sessions took place between the research fellow (CR) and team members to explain the procedure. Files containing all relevant paperwork were left in clinical areas and posters put up to publicise the study (Appendix 3). Detailed instructions were available for day unit staff who organised the ABPM (Appendix 4).

When a woman attended the department and was found to meet the trial entry criteria, she was given a patient information sheet (Appendix 5). If she declined to participate, a record

was kept of the reason for this and her care continued as normal. If she wished to participate in the trial, she was asked to sign three copies of a consent form: one to keep, one for hospital notes and one for the research record (Appendix 6). She then underwent ABPM. The research fellow was informed by telephone that the patient had been recruited to the trial and an addressograph label placed in a notebook kept by the ABPM computer, and the patient was given a patient identification number (PIN).

Sequential opaque sealed envelopes were pre-prepared by the research fellow, labelled externally with the PIN. Participants were randomized using a random number table.[237] In the envelope was placed a piece of paper on which was written Group A (even numbers in the random number table including 0), or Group B (odd numbers in the table). The patient and midwife performing ABPM were blinded as to the randomization status until after completing the monitoring. After completion of monitoring, the envelope was opened by the research fellow in a separate location to the patient before processing the results. Those in Group A had their ABPM recording revealed to the clinical team. The obstetrician was able to request further recordings if needed. Women in Group B had the results of the recording concealed from the clinical team.

The results of the ABPM were then downloaded onto the computer. If allocated to Group A (revealed), a hard copy of the results was sent immediately to the referring clinician, with a covering letter (Appendix 7). A further copy of the results was filed in the case notes so all members of the team had access to it, and a third copy kept by the research fellow for reference. If allocated to Group B (concealed), the clinician was informed of this by letter (Appendix 7). All women had ongoing care and management by their own consultant.

The research fellow checked if the 24-hour mean in a patient in the concealed group was greater than 170/110; if this occurred the patient was to be excluded from the trial and the clinician informed of the results. All downloaded ABPM results in Group B (concealed) were kept in a locked filing cabinet in a non-clinical area. The computerised results were not accessible to the clinicians caring for the patient.

A sticker was placed on the outside of all case notes and the hand-held maternity record, with the patient's permission, stating that they were taking part in the ABPM trial and which group they were in. Validation of the randomization procedure was carried out by examining notes to ensure ABPM results in the concealed group were not available to the clinical team. A Trust Research Investigators File was kept by the research fellow with all documentation related to the trial, including consent form copies, a master randomization list, screening log for those declining to take part, and a recruitment/randomization log.

Monitors and Ambulatory Monitoring Process

The SpaceLabs ambulatory blood pressure monitor 90207 was used. These oscillometric devices have been validated for use in pregnancy.[115] All monitors were serviced regularly and checked for accuracy at the beginning, halfway through and at the end of the trial. The correct size of BP cuff was applied to the patient's non-dominant arm by a trained midwife (Figure 4.1). The monitor display was disabled so that the patient could not see her own readings. Monitors were programmed with the proprietary software on a personal computer. A full 24 hours of blood pressure monitoring was carried out if the patient was able to tolerate this. Blood pressure readings were taken every 30 minutes.

After confirming that the device was working correctly, the patient either returned home or returned to the ward environment, to continue her normal routine. Once the period of recording was complete, the monitor data were downloaded onto the same computer. The result was processed as above (randomization and intervention).

Figure 4.1: ABPM monitor in situ (photograph included with written consent of patient and member of staff)

Data collection, outcome measures and definitions

The primary objective of the trial was to discover if ABPM allowed the treating clinicians to target interventions in women at higher risk, by identifying women at lower risk (with white coat hypertension or mild hypertension). Four primary outcome measures were chosen and are shown in Table 4.1, along with the secondary outcome measures:

Table 4.1 Outcome measures

Primary outcome measures	**Secondary outcome measures**
Admitted for hypertension	Preterm delivery
Antihypertensive medication	Birth weight <2.5 kg
Induction of labour (IOL) for hypertension	Admission to NNU
Caesarean section	Outpatient attendances (clinic and day unit)
	Community attendances
	No. of inpatient admissions
	No. of admissions for BP
	Length of inpatient stay: antenatal, postnatal
	Patient satisfaction with ABPM (overall)

Initial patient details available at the time of recruitment were recorded prospectively from the patient case notes by the research fellow onto a proforma (Appendix 8). This information was then entered onto an Excel computer database, designed with the supervisor, with details of clinical recordings of blood pressure and ABPM measurements. Further antenatal and outcome data were recorded onto the proforma directly from patient case records, and then entered onto the computerised database during the pregnancy and after delivery.

Once the details for each patient were entered onto the computerised database, they were cross-checked manually with the proforma for each patient. Any queries were discussed with the thesis supervisor. He also checked the Excel spreadsheet data. Any seemingly spurious or extreme values were double-checked with the proforma and hospital case-notes. The range of values for each piece of data used was checked with Excel to aid identification of incorrect entries. The items of data collected are shown in Appendix 8.

The patients were identified throughout by their allocated PIN/case number. Age was that at the date of last menstrual period. The body mass index was calculated by dividing booking weight in kilograms by height in metres^2. Ethnicity was allocated as self-reported on the maternity hand-held records (West Midlands patient held record version 1.1, based on an original design by Rupert Fawdry, modified by the West Midlands Regional Perinatal Audit.) Primiparous patients were defined as those who had not delivered a baby over 24 weeks gestation. Estimated date of delivery was calculated from ultrasound data. Gestation was entered in days. The diagnosis of hypertensive disorder was made in retrospect using criteria as defined by Davey and MacGillivray (Table 2.1).[53]

Admission to hospital was defined by an overnight stay, otherwise these were classified as ward attendances. To quantify length of stay, any part of a 24-hour period spent in hospital during an admission was included as a day. Preterm delivery was defined as birth before 37 completed weeks (258 days or less). Growth restricted babies were defined as a birth weight less than the 10th centile, adjusted for gender and gestation.[215]

Patient Questionnaire

In order to assess the woman's experience of the monitoring, a patient questionnaire was sent to all participants (Appendix 9). A stamped addressed envelope was included for return. Participants were identified by their PIN on the questionnaire. The responses on the questionnaires were divided into discrete variables and analysed using percentages in each response group. A section for free text comments was also included.

Statistical Considerations

Shown below in Table 4.2 are the power calculations for the various outcome measures chosen as indicators of success for the group with revealed ABPM records. The baseline rates for the outcome measures were based on data for the hospital. The overall incidence of white coat hypertension in the pregnant population in published studies is around 10-20% (see section 1.4.3). By detecting white coat hypertension, we proposed that rates of intervention might decrease by 10-15% as shown in the Table.

Generalisability (external validity) is the extent to which results of a study can be generalised to different circumstances.[238] We aimed to conduct a pragmatic study of well-defined outcomes relating to a standard intervention (ABPM). Applicability of the results of the study would be a matter of judgement for example in very different populations (eg different ethnic composition, high-risk tertiary level patients). However, a large portion of maternity care is conducted in district hospitals such as the setting for this study, and results would be generalisable to the majority of the obstetric population.

Table 4.2. Power calculations

Change in Outcome Measure		Confidence Interval	Power	No of participants in each arm
Admission rate 70%-55%	(15%)	95%	80%	175
Induction rate 60%-45%	(15%)	95%	80%	186
Caesarean rate 40%-30%	(10%)	95%	80%	351

The primary analysis was intention-to-treat and involved all patients who were randomly assigned. Means and standard deviation (SD), and medians were calculated for baseline characteristics and continuous variables. Risk difference was calculated with 95% confidence intervals for categorical outcome variables, with χ^2 test for significance. Analysis of variance (ANOVA) or the Mann-Whitney test were used for continuous variables. The Minitab statistical package was used for data analysis.[216]

Ethical approval

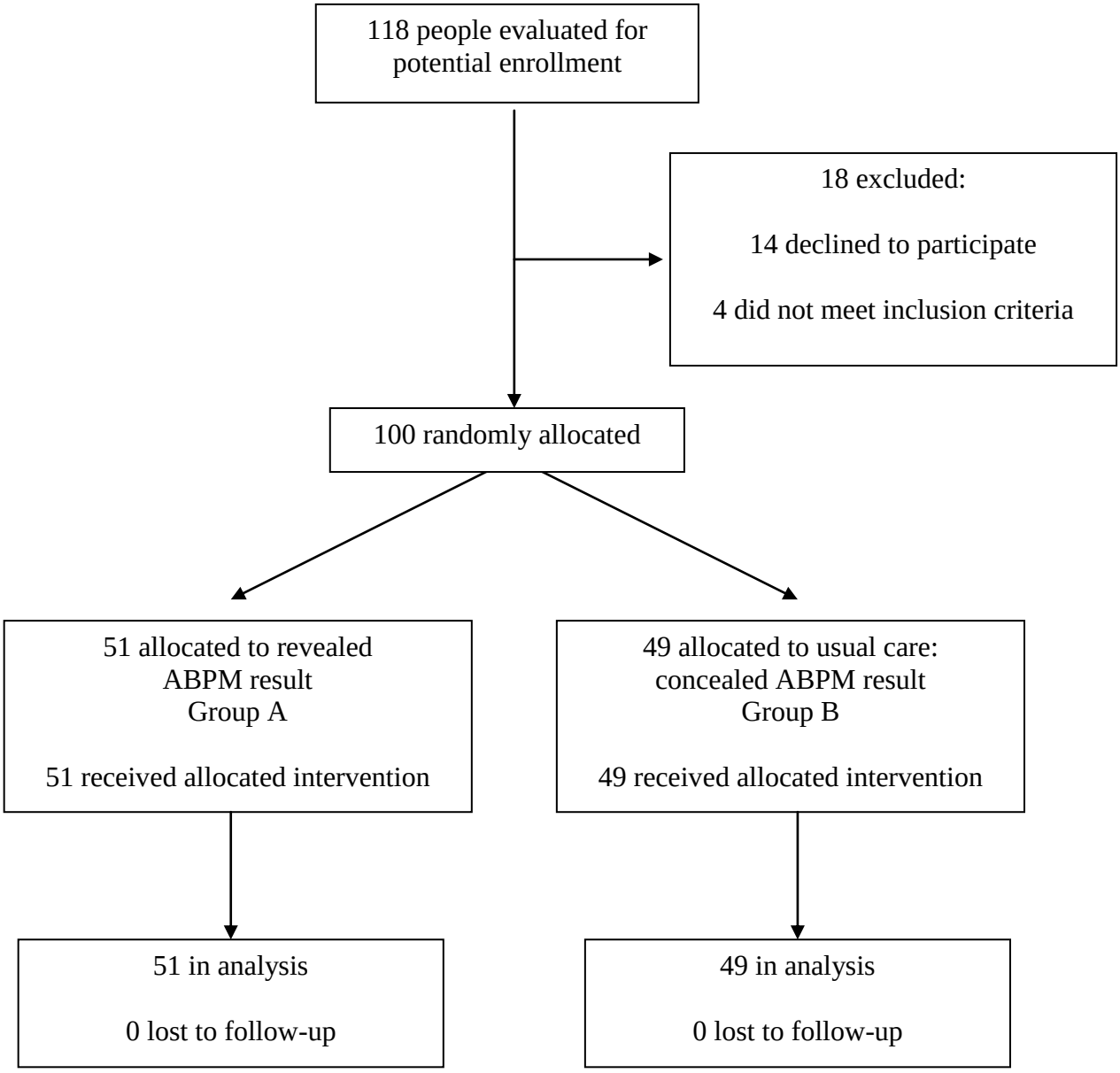
Ethical approval was obtained from the North Birmingham Research Ethics Committee in February 2002 (Appendix 10).

4.4 RESULTS

Results are presented as recommended by the Revised CONSORT (Consolidated Standards of Reporting Trials) Statement for Reporting Randomized Trials.[238] Figure 4.2 shows the flowchart describing the flow of participants through each stage of the trial. 118 women were asked to take part in the trial. Eighteen were excluded. Of these, 14 women declined to take part for reasons such as limited time or not wanting to be monitored. Four women did not meet inclusion criteria: two did not speak English and no interpreter was available to take consent, one was diabetic and one had ABPM already performed in the pregnancy.

A total of 100 women were randomized over the study period from March 2002 to December 2003 (22 months). Fifty-one women were allocated to Group A and 49 to Group B. All underwent the intervention of ABPM. The median time of ABPM recording was 23 hours and 28 minutes. All women received the allocated randomized intervention of revealing or concealing the results, with no violation of the protocols detected. No women were lost to follow-up and all data needed to analyse primary outcomes were retrieved. There were no adverse events or side effects in either group.

Figure 4.2. Flow diagram of participants in trial



Baseline demographic and clinical characteristics of each group are shown in Table 4.3.

Table 4.3. Baseline characteristics of trial groups

Characteristic	**Group A (n = 51)**	**Group B (n = 49)**
Mean age ± SD, *years*	30.2 ± 6.0	29 ± 5.0
Mean body mass index ± SD, kg/m^2	26.2 ± 4.3	27.3 ± 6.0
Mean booking blood pressure ± SD, *mmHg*		
Systolic	119 ± 13	120 ± 12
Diastolic	75 ± 11	73 ± 10
Parity, *n (%)*		
0	32 (62)	32 (65)
1	11 (22)	12 (25)
2	4 (8)	4 (8)
>2	4 (8)	1 (2)
White, *n (%)*	46 (90)	47 (96)
Mean gestation at trial entry ± SD, *days*	231 ± 39	240 ± 48
Past history, *n (%)*		
Previous pre-eclampsia	7 (13.7)	5 (10.2)
Pre-pregnancy hypertension	8 (15.7)	6 (12.2)
Previous caesarean section	9 (17.6)	5 (10.2)

SD =standard deviation

Table 4.4 shows a summary of results for each primary outcome within each group, with the estimated effect size and its precision (95% confidence interval). There was a statistically significant decrease of 23% in the rate of induction of labour for hypertension in Group A (revealed result) compared to Group B (concealed result). In view of this, further analysis was done on induction of labour. Fewer women underwent induction of labour overall in Group A compared to Group B (37.3% vs 49%), but the overall rates of induction of labour were not significantly different between the two groups (Table 4.4.) All 24 inductions in Group B were for hypertension. Thirteen women in Group A underwent induction of labour for hypertension. Of the six patients induced for other indications in Group A, four were post-term, one had pre-labour rupture of the membranes with meconium staining of the amniotic fluid, and one was for maternal choice. Details of gestation at delivery of all women undergoing induction of labour were analysed. More induced women delivered at ≥40 weeks gestation in Group A (8 of 19 women) compared to Group B (4 of 24 women): 42.1% vs 16.7%.

Table 4.4. Summary results: Primary outcomes and induction of labour (overall)

Outcome **n (%)**	**Group A (revealed)** **n = 51**	**Group B (concealed)** **n = 49**	**Risk Difference (95% CI)**	***P* value (χ-square)**
Admitted for hypertension	35 (69)	35 (71.4)	-0.03 (-0.21, 0.15)	0.760
Antihypertensive medication	26 (51)	24 (49)	0.02 (-0.18, 0.22)	0.841
Induction of labour for hypertension	13 (25.5)	24 (49)	-0.23 (-0.42, -0.05)	0.015
Induction of labour overall	19 (37.3)	24 (49)	-0.12 (-0.31, 0.08)	0.236
Caesarean section	20 (39.2)	19 (38.8)	0.00 (-0.19, 0.20)	0.964

Table 4.5 shows results for neonatal outcomes. There were no perinatal losses. Table 4.6 shows attendance and length of stay data. No differences were seen between the two groups for any of these outcomes.

Table 4.5. Summary results. Secondary outcome measures: neonatal data

Outcome **n (%)**	**Group A** **(revealed)** **n = 51**	**Group B** **(concealed)** **n = 49**	**Risk Difference** **(95% CI)**	***P* value** **(χ-square)**
Preterm delivery	11 (21.6)	5 (10.2)	0.11 (-0.03, 0.25)	0.121
Birth weight<2.5 kg	10 (19.6)	9 (18.4)	0.01 (-0.14, 0.17)	0.874
Admission to NNU	13 (25.5)	8 (16.3)	0.09 (-0.07, 0.25)	0.261

Table 4.6 Summary results. Secondary outcomes: attendance/length of stay data

Outcome: **Median**	**Group A** **(revealed)** **n = 51**	**Group B** **(concealed)** **n = 49**	**Point Estimate*** **(95% confidence intervals)**	***P* value***
Outpatient attendances: antenatal clinic *(n)*	5	4	1.0 (-1.0, 2.0)	0.380
Outpatient attendances: antenatal day unit *(n)*	3	3	-1 (-2.0, 1.0)	0.319
Community attendances *(n)*	11	9	1 (-0.001, 3.0)	0.150
Inpatient admissions *(n)*	2	2	0 (-0.0002, -0.0002)	0.293
Admissions for BP *(n)*	1	1	0 (-0.0000, 0.0001	0.934
Antenatal stay *(days)*	4	4	-0 (-1.000, 1.999)	0.682
Postnatal stay *(days)*	3	3	0 (-1.0, 1.0)	0.696

*Mann-Whitney test

As part of the trial protocol, a six week follow-up appointment was included. Only 28 women came to their appointment (14 from Group A and 14 from Group B), giving inadequate data for analysis. This is not unusual in studies of this kind; for example Brown et al reported that only 33% of patients in a study of white coat hypertension attended their postpartum follow-up appointment.[190] For the women who attended their appointment, it was generally used as an opportunity to answer any queries, provide information about hypertension in pregnancy and to remind the patient to complete the participant questionnaire (see below).

All 100 participants were sent a questionnaire in the first 6 weeks after delivery asking about their experience of ABPM. A stamped envelope addressed to the research fellow was enclosed with the questionnaire. Sixty-three women returned completed questionnaires. Fifty-nine were returned within six weeks, and the remaining four questionnaires were returned by eight weeks after posting. Of the returned questionnaires, 32 (51%) were in Group A and 31 (49%) in Group B. The questionnaire is shown in Appendix 9, and results are summarised in Table 4.7. When asked ‘If 24-hour blood pressure monitoring became part of routine pregnancy care would you be willing to have it again in a future pregnancy?’ 56 women (89%) answered yes, 2 (3%) were unsure and 5 (8%) said no.

Table 4.7 Summary of responses to participant questionnaire

Question	Group	Answer: n (%)					
		No	**Slight**	**Moderate**	**Severe**	**NR**	**Total**
Use of arm limited	A	5 (16)	21 (66)	6 (19)	0	0	32
	B	4 (13)	18 (58)	8 (26)	0	1 (3)	31
	All	9 (14)	39 (62)	14 (22)	0	1 (2)	63
Discomfort from cuff	A	6 (19)	17 (53)	7 (22)	2 (6)	0	32
	B	4 (13)	19 (61)	7 (23)	0	1 (3)	31
	All	10 (16)	36 (57)	14 (22)	2 (3)	1 (2)	63
Daily activities limited	A	8 (25)	19 (59)	4 (13)	1 (3)	0	32
	B	10 (32)	14 (45)	5 (16)	1 (3)	1 (3)	31
	All	18 (29)	33 (52)	9 (14)	2 (3)	1 (2)	63
Monitor noise disturbing	A	11 (34)	12 (38)	9 (28)	0	0	32
	B	12 (39)	9 (29)	7 (23)	2 (3)	1 (3)	31
	All	23 (37)	21 (33)	16 (25)	2 (3)	1 (2)	63
Sleep pattern disturbed	A	5 (16)	14 (44)	10 (32)	3 (9)	0	32
	B	10 (32)	6 (19)	7 (23)	6 (19)	2 (6)	31
	All	15 (24)	20 (32)	17 (27)	9 (14)	2 (3)	63
Would have ABPM again		**Yes**		**No**	**Not sure**		**Total**
	A	30 (94)		2 (6)	0		32
	B	26 (84)		3 (10)	2 (6)		31
	All	56 (89)		5 (8)	2 (3)		63
Comments		**Positive**		**Negative**	**Neutral**		**Total**
	A	6 (67)		2 (22)	1 (11)		9
	B	7 (44)		8 (50)	1 (6)		16
	All	13 (52)		10 (40)	2 (8)		25

NR = no response

Women were asked to enter further comments as free text. Comments were made on 25 out of 63 (40%) forms and are summarised in Table 4.7 above. Thirteen comments (52%) were positive, 10 (40%) were negative and 2 (8%) were neutral. A more selection of themes and comments are summarised in Table 4.8.

Table 4.8 Sample of free-text responses to participant questionnaire

Theme	Example	Group
Usefulness of technique	'…gave a clearer overview of my blood pressure than the usual one-off reading…'	A
	'…worth it to know that a true picture of your blood pressure can be built up without having to stay in hospital.'	A
	'…the doctors found out my true blood pressure. If a midwife was to come and take my b/p it was sometimes higher because I became anxious.'	A
Taking part in research	**'**I would do it again if it can help similar women when pregnant.'	B
	'I was pleased to participate'	A
	'Just happy to help.'	A
Disadvantages	'…tightness of the cuff made holding, carrying things very difficult.'	B
	'…another check a couple of minutes later unexpectedly – this was frustrating.'	B
	'…it was cumbersome.'	A
	'…wouldn't want to go shopping with it..noisy…embarrassing'	B
	'…very uncomfortable…the metal part dug into my arm.'	B
Suggestions	'…driving was impaired I feel this should be stressed before issuing…'	B
	'…would choose if possible to use the monitoring when I wasn't at work…pupils found it distracting…'	B

4.5 DISCUSSION

This is the first randomized controlled trial of ABPM in pregnancy. The aim of this study was to perform a pragmatic trial of the use of ABPM as it is currently used in hypertensive pregnancies in the setting of a District General Hospital. Patients remained under the care of their booked consultant, and this team controlled patient management. The only difference between the two groups was the availability of the results of ABPM. The groups were comparable in their baseline demographic and patient characteristics (Table 4.3). The flow of patients was demonstrated as per the CONSORT guidelines for reporting of randomized trials. All patients conformed to the trial protocol and no women were lost to follow-up (Figure 4.2). A full CONSORT checklist is attached in Appendix 11. We have successfully demonstrated that such a trial is practical.

The protocol specified four primary outcomes for the trial. The CONSORT statement for reporting randomized trials defines the primary outcome as the prespecified outcome of greatest importance.[238] It states that having more that one or two primary outcomes can lead to problems of interpretation due to multiplicity of analyses, and is not recommended. Multiple analysis of the same data increases the risk of a Type I error, attributing a difference to an intervention when this is by chance, leading to a false-positive finding.

The only statistically significant different outcome between the groups was in rates of induction of labour for hypertension, with lower rates in the group with revealed results (25.5% vs 49%, p=0.015). This is consistent with the hypothesis underpinning this work, that ABPM would avoid unnecessary rates of intervention. The decreased rate of induction for

hypertension could be explained by reassuring results of 24 hour blood pressure monitoring (compared to conventional measurements), which were not available in the concealed group.

When analyzing the overall induction rate, it was still lower in Group A compared to Group B (37.3% vs 49%). However, this difference was not statistically significant (p=0.236). When the inductions of labour in the Group B (concealed) group were analysed, all 24 were done for the indication of hypertension. In the women in the Group A (revealed) group, 13 of the 19 inductions were done for raised BP. The remainder were for post-term (n=4), pre-labour ruptured membranes (n=1) and maternal choice (n=1). These results do suggest that there is a trend for clinicians to be reassured by ABPM results and allow pregnancies to continue for longer without induction of labour for hypertension. This premise is supported by the fact that more women who were induced in Group A delivered at a gestation of ≥40 weeks than in Group B (42% vs 16%).

An alternative explanation for the results on induction might be that clinicians chose to record the indication for induction in Group B (concealed) as hypertension in preference to other reasons. The higher rates of induction for hypertension in Group B would then simply reflect a raised risk of 'labelling' women as hypertensive and documenting this as the main reason for their decision to intervene. However, this would actually support our hypothesis that ABPM would decrease intervention by detecting women with white coat hypertension, reassuring clinicians who would not label the pregnancies as hypertensive. The information on gestation at delivery in women who were induced is of interest, as women in Group B were generally induced before 40 weeks. This suggests clinicians were not simply 're-labelling' women being induced at post-term as hypertensive, and that the recorded indication for induction is a true representation of the clinician's decision.

There was no significant increase in the rates of adverse perinatal outcomes examined: rates of preterm delivery, low birth weight and neonatal admission did not differ between the two groups (Table 4.5).

In any trial of an intervention the experience of the participants should be assessed. Previous authors have published rates of complication and patient acceptability of ABPM devices. In a study of 219 non-pregnant patients, only four had complications; in all cases this was petechiae distal to the cuff.[239] In an evaluation of the SpaceLabs 90207 monitor in 120 pregnant and postpartum women, over half reported sleep disturbance and significant discomfort.[240] The device was judged 'acceptable' by 74% at first use. The same monitor was evaluated by 110 women in a 2004 report, and problems with sleep were a major cause of dissatisfaction: 79% of patients reported a degree of sleep disturbance. [241]

In our patients, the results in Table 4.7 show similar findings, with only 24% reporting that their sleep was not disturbed, and 14% describing disturbance as 'severe'. Limitation of daily activities was reported to some degree by 69% of patients. There were a similar number of questionnaires returned for each group. It is notable that more patients in Group B (concealed) than Group A (revealed) entered comments (16 vs 9), and that 50% of these were negative compared to 22% of the Group A comments. The patients were aware of their group allocation once ABPM was complete. The group with concealed results did not gain personally from the test, which might increase the chance of negative feedback. However, there was still comment from Group B participants on being happy to take part in research, and 7 of 13 (54%) of all positive comments were from this group. Overall, free text comments were more positive than negative, with a good understanding of potential

advantages of the technique. A willingness to repeat ABPM if recommended in future pregnancy was reported by 89% of the participants.

The literature published so far in the field of ABPM in pregnancy has been extensively reviewed in Chapter 1. There are no randomized trials with which to compare this work. However, the findings are consistent with previous authors who report that ABPM is useful particularly in assessing women who may have white coat hypertension, which would not warrant obstetric intervention but is only diagnosed if ABPM is performed. The consultants in our hospital were familiar with the use of ABPM and interpretation of results, and should be experienced at taking the results into account when deciding on management. In other settings, education would be needed for clinicians particularly on the normal ranges of ABPM in the different trimesters of pregnancy.

When designing a randomized study of a diagnostic test such as blood pressure monitoring several factors need to be considered. Firstly, it is not possible to blind the patient or staff to the fact that the test is being performed. We therefore blinded the staff and patient to the group allocation until the investigation was complete, and blinded clinicians and participant to the result in the concealed group. Secondly, we deliberately performed the ABPM in both groups of patients. This was to avoid the confounding effect of two attendances at hospital at the day unit (for application and downloading of the monitoring) as an opportunity for staff to assess a patient. If ABPM was found to be helpful one could argue that the extra attendance, not the monitoring itself, was responsible. However, in our study all patients attended for monitoring. Finally, it was also an ethical consideration, as very raised results were to be communicated regardless of the group allocation.

We were guided by the CONSORT statement for reporting randomized trials in documenting our results, and were able to conform to the standards set.[238] However, the intervention in our randomized trial is unusual because it is a diagnostic test, rather than a treatment or management strategy. The level of blood pressure on ABPM is a means of diagnosing hypertensive disorder and contributing to allocation of risk. It also is directly related to detection of the complications of worsening hypertension (such as superimposed pre-eclampsia in chronic hypertension), a diagnosis which can also be seen as an outcome. We used concrete outcomes to assess the use of ABPM such as induction of labour, caesarean section and birth weight of the baby. This provides a separation between the randomized 'intervention' of the ABPM result and outcomes to be assessed. It also prioritises outcomes which are of most interest to clinicians and their patients.

In a series of papers on the evidence base of clinical diagnosis in the BMJ, the authors of the introductory article (Knottnerus et al) state that 'the methodology of diagnostic research lags behind that for evaluating treatment.' [242] Diagnostic investigations have the following objectives: increasing certainty of presence or absence of disease, supporting clinical management, assessing prognosis, monitoring clinical course and measuring fitness. All the first four objectives apply to ABPM. The choice of study design in diagnostic research varies with the aims of that study. For example, to assess the diagnostic accuracy of a test, cross sectional studies with reference to the 'gold standard' are needed. This has been described in the studies of ABPM in pregnancy, outlined in Section 1.4.3 above, which compare it to the use of conventional mercury BP devices, using techniques such as sensitivity and specificity, and the area under a receiver operator characteristic curve.

The most important evaluation of a diagnostic test involves the health outcomes after management informed by the test.[243] To study the impact of a test on decision-making and outcomes, the standard method is quoted as the randomized controlled trial. This method is superior to an observational cohort study, where both groups may not be comparable at baseline entry. The value of the test under investigation can be assessed (in comparison to either the usual procedure or no test), in providing potential improvements in diagnostic accuracy, management and prognosis. Knottnerus et al describe a 'variant' where the index test is used on all subjects, with randomized disclosure of the results to the clinical team caring for the patient (if ethical). The authors describe this as an 'ideal placebo procedure' for the patient. This is the design of our research study.

To complement the CONSORT statement for reporting randomized trials, the STARD (Standards for Reporting of Diagnostic Accuracy) Initiative was published in 2003.[244] A checklist and flow diagram was produced, but these are particularly relevant to reporting studies of diagnostic accuracy such as laboratory tests. The randomized controlled trial we conducted was more suited to the CONSORT guideline,

The main limitations of our study relate to the power calculations and number of patients recruited. We did not enroll as many people in the trial as recommended by the power calculations. Unfortunately the other participating centre withdrew due to logistical problems. A significant decrease in rates of induction of labour for hypertension was seen in the group with revealed ABPM results. Although overall rates of induction were also reduced in this group, this did not reach statistical significance. The lack of adverse effects of perinatal outcomes may be secondary to the small sample size and should be interpreted with caution.

We also recruited a deliberately heterogeneous population with broad inclusion criteria. Women with various disorders at different gestations were included, and this may have placed ABPM at a disadvantage. Other research has suggested that ABPM has a greater benefit in women with chronic hypertension. This is also consistent with findings in the non-pregnant population, where ABPM confers the greatest benefit in predicting cardiovascular disease in later life. Chronic hypertension is a particularly high-risk state in pregnancy, possibly due to early end-organ damage and/or increased vascular resistance. ABPM, as a better predictor of cardiovascular outcome, may be most useful in assessing this group of patients during pregnancy. In view of the positive findings of observational studies of ABPM in women with suspected hypertension in early pregnancy[190], a randomized trial in this group would provide useful evidence on the use of ABPM, particularly relating to identification of white coat hypertension.

Another reason for the lack of an effect might be the elements of ABPM reported to clinicians in the study, ie daytime, night-time and 24-hour means for systolic, diastolic and mean arterial pressure, along with raw data. No further modeling of the data was performed. Other measures described in section 1.4.3, such as blood pressure load, might be more powerful measures when predicting outcomes in pregnancy. Finally, the clinicians in the study, although familiar with the technique of ABPM, may not have used these results in the most effective way.

In summary, we have shown that it is feasible to conduct a randomized controlled trial of the diagnostic technique of ABPM, and report here the first such trial of ABPM in pregnancy. Although patient acceptability is good, rates of sleep disturbance and discomfort cannot be disregarded, and it is important to establish in pragmatic practice the potential advantage of

decreasing rates of intervention without adversely affecting outcomes. Further studies with a similar design and larger numbers of participants in specified diagnostic groups should provide the answer to these questions, with the option of combining results in a meta-analysis for robust evidence in this important area of obstetric practice.

CHAPTER 5:

CONCLUSIONS AND RECOMMENDATIONS

5.1 SUMMARY OF FINDINGS

This thesis begins with a review of blood pressure measurement outlining the history of the technique, along with potential sources of inaccuracies inherent in conventional measurement, including device faults and human error. The incidence and implications of high blood pressure in pregnancy are discussed in section 1.3. There are now established clinical and research definitions which should aid work in the field. The importance of this common pregnancy complication and its role in relation to outcomes such as maternal mortality and morbidity, perinatal loss, preterm delivery and growth restriction in the fetus is emphasised. However, there are significant gaps in knowledge of the pathophysiology of the hypertensive disorders of pregnancy which hamper efforts to improve clinical care.

The potential of ambulatory blood pressure monitoring (ABPM) to provide more reliable measurements, predicting outcomes more effectively and thus improving allocation of risk, is discussed in section 1.4. There is increasing evidence supporting the use of ABPM in non-pregnant individuals, especially in assessment of patients suspected of having white coat hypertension. Improved prediction of outcomes such as end-organ damage is now evident from large-scale trials. These findings mirror the relevant areas in obstetric practice of improved diagnosis and identifying high risk pregnancy.

To provide reliable readings in pregnancy formal validation of devices is advised. This is reviewed in section 1.4.2. There is proven need for caution in severe pre-eclampsia, as several studies revealed unreliable results for ABPM in these women. An exhaustive search and review of the literature has revealed only eight papers publishing ten validation studies using recommended protocols in pregnancy, and only two devices passed. One of these

devices, the SpaceLabs 90207, was used in the research in this thesis. It is not unusual for studies of ABPM in pregnancy to quote validation studies in which the device actually fails. However, the relevance of a small number of readings at rest compared to mercury device readings, in a monitor designed to be used for multiple readings while a patient is ambulatory over 24 hours, can be questioned. The practical applications of use in the clinical situation and the potential for improving patient care and outcomes are the ultimate test of the technique.

This is examined in section 1.4.3 with a review of the literature available on the use of ABPM in pregnancy (Table 1.4). All studies are observational, cohort or case-controlled studies; no randomized trials were identified. The normal values and patterns of ABPM in normotensive and hypertensive pregnancy have been established. Early hopes for screening normal pregnancies for risk of hypertension in pregnancy or pre-eclampsia using patterns such as loss of nocturnal 'dip' were not confirmed, as studies showed disappointing positive predictive values. Some authors have shown reasonable prediction of hypertensive outcomes using ABPM either in combination with indices in high risk women (such as uterine artery Doppler), or with complex computerised assessment, or in diabetic women. However, the results are inconsistent.

When assessing a hypertensive population for prediction of specific outcomes such as poor fetal growth, proteinuria, preterm delivery, and severe hypertension, ABPM has compared favourably to conventional BP measurement. It also has a continuous inverse relationship with fetal birth weight in the general obstetric population. It is in the area of white coat and chronic hypertension that the most interesting results emerge, with initial scepticism in some authors giving way to good evidence that in suspected essential hypertension in early

pregnancy, a third of women can be identified as having white coat hypertension. There are better outcomes in this group with potential for reducing interventions such as anti-hypertensive medication. The reviews and guidelines (Table 1.5) of ABPM in the literature echo the above findings.

In Chapter 2, outcomes of pregnancies in hypertensive women attending a specialist antenatal clinic were examined, with particular reference to 317 women with chronic hypertension. Compared to the hospital population, all hypertensive women had a significantly increased rate of Caesarean section and (with the exception of those with gestational hypertension) a baby born preterm or small for gestational age. Perinatal mortality rates were very high, and were increased in Black women, and significantly raised in Asian compared to White women (83.3:1000 vs 28.0:1000). In chronic hypertension, stillbirth rates were raised in Asian vs White women (102:1000 vs 11:1000). Superimposed pre-eclampsia raised perinatal mortality rate significantly to 115.9:1000.

Mean gestation at birth of stillborn babies in chronic hypertensive pregnancies was 28 weeks, and 88.2% were growth-restricted. Nearly one in five Asian women with chronic hypertension booked after 20 weeks gestation, suggesting lack of early pregnancy care might contribute to worse outcomes in this group. In conclusion, this study confirms poor outcomes particularly in chronic hypertension, which are worse in women of Black and Asian ethnicity. Fetal growth restriction is an important risk and is linked to intra-uterine death. Reports in the literature of outcomes in hypertension in Asian women are very limited; work from this database is important in publicising these figures.

Any mechanism of improving these outcomes deserves investigation. To this end, Chapter 3 assesses the predictive value of ABPM for important outcomes. Using regression analysis to compare it to conventional BP measurement, ABPM predicted development of proteinuria, gestation and weight at birth with greater accurately. This confirms previous research findings. This work also found that the technique of ABPM was viable in our District General Hospital setting. Following this initial assessment of ABPM, we undertook the first randomized controlled trial of ABPM in pregnancy.

In section 4.5 the area of diagnostic research is reviewed. Randomized controlled trials are recommended to assess diagnostic techniques as they are used in the clinical area. One proposed study design is the 'ideal placebo procedure' of using the 'test' on all subjects with randomized disclosure of results. This design is used in our study, which showed that a pragmatic prospective randomized controlled trial of ABPM in hypertensive pregnancies is possible. We randomized 100 women to either revealed or concealed ABPM result. In the women with the revealed result, induction of labour for hypertension significantly decreased by 23%. Although overall rates of induction were also reduced in this group, this did not reach statistical significance. There were no other differences in other outcomes between the groups. A patient questionnaire showed good understanding of the potential advantages of the technique, and 89% would be willing to undergo ABPM in a future pregnancy. However, there are issues with self-reported sleep disturbance and discomfort, emphasising the need for good evidence behind the request for women to undergo this monitoring.

The hypothesis underlying the trial was that identification of women with white coat hypertension might reassure clinicians and limit intervention to those women with genuinely raised BP in pregnancy. The reduced rate of inductions for hypertension would support this.

Unfortunately we did not recruit the numbers of women needed according to the power calculations. There was also a heterogeneous population of women within the trial which might 'dilute' the possible effect of ABPM on outcomes.

5.2 RECOMMENDATIONS FOR FUTURE RESEARCH

The lack of robust validation of ABPM devices in common usage is of concern. Relevant bodies such as the International Society for the Study of Hypertension in Pregnancy and the British Hypertension Society should advise on processes for validation and testing of these devices, with investigation of the possibility of testing the devices during normal use.

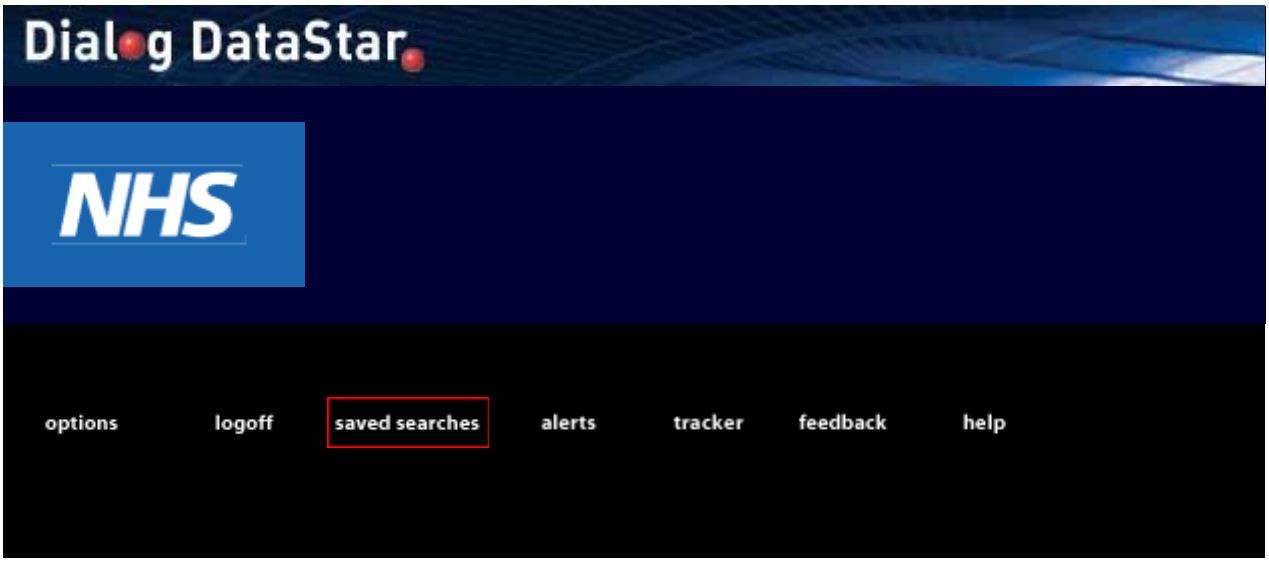
The very high perinatal mortality rates found in the review of the database of hypertensive pregnancies and outcomes are at least equivalent to those in maternal diabetes. The Confidential Enquiry into Maternal and Child Health (CEMACH) has conducted a confidential enquiry into the care of diabetic women and published recommendations in this field. We propose that management of women with chronic hypertension in pregnancy would be a suitable topic for a further enquiry, with particular focus on women from Black and Asian ethnic backgrounds.

There is good potential for the use of ABPM in chronic hypertension, particularly to identify women with white coat hypertension in early pregnancy, who have better outcomes and can safely have less intervention. We have shown that randomized trials of ABPM are viable; a study of pregnant women with hypertension at first presentation, especially with uncertain diagnosis, would confirm this, while ensuring that there are no adverse effects of the monitoring.

APPENDICES

APPENDIX 1: LITERATURE SEARCH

A formal systematic search was also conducted with the aid of a clinical librarian as outlined below, with the aim of identifying studies of ABPM in pregnancy, and general reviews of hypertension in pregnancy to identify recent advances and important studies.



Saved Searches

You have the following Saved Searches.
To run a Saved Search, select it and click the **Run Search** button.
Click **Delete** to delete a Saved Search.

Name	Search strategy
GENERAL HT SEARCH MEDLINE 21 09	1. SEARCH: HYPERTENSION.TI. 2. SEARCH: HYPERTENSION.W..MJ. 3. SEARCH: HYPERTENSION-PREGNANCY-INDUCED.MJ.

	4. SEARCH: 1 OR 2 OR 3 5. SEARCH: PREECLAMP$4.TI. 6. SEARCH: PRE-ECLAMP$4.TI. 7. SEARCH: (PRE ADJ ECLAMP$4).TI. 8. SEARCH: PRE-ECLAMPSIA.MJ. 9. SEARCH: 5 OR 6 OR 7 OR 8 10. SEARCH: 4 OR 9 11. SEARCH: PREGNAN$5.TI,AB. 12. SEARCH: PREGNANCY.W..MJ. 13. SEARCH: 11 OR 12 14. SEARCH: 10 AND 13 15. SEARCH: 14 AND LG=EN 16. SEARCH: 15 AND REVIEW=YES 17. SEARCH: 15 AND PT=META-ANALYSIS 18. SEARCH: 15 AND (CLINICAL-TRIALS# OR PT=CLINICAL-TRIAL#) 19. SEARCH: 16 OR 17 OR 18
HYPERTENSION GENERAL EMBASE 21 09	1. SEARCH: HYPERTENSION.TI. 2. SEARCH: HYPERTENSION.W..MJ. 3. SEARCH: MATERNAL-HYPERTENSION.MJ. 4. SEARCH: 1 OR 2 OR 3 5. SEARCH: PREECLAMP$4.TI. 6. SEARCH: PRE-ECLAMP$4.TI. 7. SEARCH: (PRE ADJ ECLAMP$4).TI. 8. SEARCH: PREECLAMPSIA.W..MJ. 9. SEARCH: 5 OR 6 OR 7 OR 8 10. SEARCH: 4 OR 9 11. SEARCH: PREGNAN$5.TI,AB. 12. SEARCH: PREGNANCY.W..MJ. 13. SEARCH: 11 OR 12 14. SEARCH: 10 AND 13 15. SEARCH: 14 AND LG=EN 16. SEARCH: 15 AND REVIEW=YES 17. SEARCH: 15 AND PT=META-ANALYSIS

	18. SEARCH: 15 AND (CLINICAL-TRIALS# OR PT=CLINICAL-TRIAL#) 19. SEARCH: 16 OR 17 OR 18
HYPERTENSION IN PREGNANCY GENERAL 20 09 07	1. SEARCH: HYPERTENSION.TI. 2. SEARCH: HYPERTENSION.W..MJ. 3. SEARCH: HYPERTENSION-PREGNANCY-INDUCED.MJ. 4. SEARCH: 1 OR 2 OR 3 5. SEARCH: PREECLAMP$4.TI. 6. SEARCH: PRE-ECLAMP$4.TI. 7. SEARCH: (PRE ADJ ECLAMP$4).TI. 8. SEARCH: PRE-ECLAMPSIA.MJ. 9. SEARCH: 5 OR 6 OR 7 OR 8 10. SEARCH: 4 OR 9 11. SEARCH: PREGNAN$5.TI,AB. 12. SEARCH: PREGNANCY.W..MJ. 13. SEARCH: 11 OR 12 14. SEARCH: 10 AND 13 15. SEARCH: 14 AND LG=EN 16. SEARCH: 15 AND REVIEW=YES 17. SEARCH: 15 AND PT=META-ANALYSIS 18. SEARCH: 15 AND (CLINICAL-TRIALS# OR PT=CLINICAL-TRIAL#) 19. SEARCH: 16 OR 17 OR 18
ABPM SEARCH 20 09 07	1. SEARCH: ABPM.TI,AB. [MEDL] 2. SEARCH: (AMBULATORY ADJ BLOOD ADJ PRESSURE).TI,AB. [MEDL] 3. SEARCH: BLOOD-PRESSURE-MONITORING-AMBULATORY.MJ. [MEDL] 4. SEARCH: PREGNAN$4.TI,AB. [MEDL] 5. SEARCH: PREGNANCY.W..MJ. [MEDL] 6. SEARCH: 1 OR 2 OR 3 [MEDL]

	7.	SEARCH: 4 OR 5	[MEDL]
	8.	SEARCH: 6 AND 7	[MEDL]
	9.	SEARCH: 8 AND LG=EN	[MEDL]
	10.	SEARCH: ABPM.TI,AB.	[EMED]
	11.	SEARCH: (AMBULATORY ADJ BLOOD ADJ PRESSURE).TI,AB.	[EMED]
	12.	SEARCH: BLOOD-PRESSURE-MONITORING-AMBULATORY.MJ.	[EMED]
	13.	SEARCH: PREGNAN$4.TI,AB.	[EMED]
	14.	SEARCH: PREGNANCY.W..MJ.	[EMED]
	15.	SEARCH: 10 OR 11 OR 12	[EMED]
	16.	SEARCH: 13 OR 14	[EMED]
	17.	SEARCH: 15 AND 16	[EMED]
	18.	SEARCH: 17 AND LG=EN	[EMED]
HYPERTENSION IN PREGNANCY GENERAL EMBASE 20 09 07	1.	SEARCH: HYPERTENSION.TI.	[MEDL]
	2.	SEARCH: HYPERTENSION.W..MJ.	[MEDL]
	3.	SEARCH: HYPERTENSION-PREGNANCY-INDUCED.MJ.	[MEDL]
	4.	SEARCH: 1 OR 2 OR 3	[MEDL]
	5.	SEARCH: PREECLAMP$4.TI.	[MEDL]
	6.	SEARCH: PRE-ECLAMP$4.TI.	[MEDL]
	7.	SEARCH: (PRE ADJ ECLAMP$4).TI.	[MEDL]
	8.	SEARCH: PRE-ECLAMPSIA.MJ.	[MEDL]
	9.	SEARCH: 5 OR 6 OR 7 OR 8	[MEDL]
	10.	SEARCH: 4 OR 9	[MEDL]
	11.	SEARCH: PREGNAN$5.TI,AB.	[MEDL]
	12.	SEARCH: PREGNANCY.W..MJ.	[MEDL]
	13.	SEARCH: 11 OR 12	[MEDL]
	14.	SEARCH: 10 AND 13	[MEDL]
	15.	SEARCH: 14 AND LG=EN	[MEDL]
	16.	SEARCH: 15 AND REVIEW=YES	[MEDL]
	17.	SEARCH: 15 AND PT=META-ANALYSIS	[MEDL]
	18.	SEARCH: 15 AND (CLINICAL-	[MEDL]

		TRIALS# OR PT=CLINICAL-TRIAL#)	
	19. SEARCH:	16 OR 17 OR 18	[MEDL]
	20. SEARCH:	HYPERTENSION.TI.	[EMED]
	21. SEARCH:	HYPERTENSION.W..MJ.	[EMED]
	22. SEARCH:	MATERNAL-HYPERTENSION.MJ.	[EMED]
	23. SEARCH:	20 OR 21 OR 22	[EMED]
	24. SEARCH:	PREECLAMP$4.TI.	[EMED]
	25. SEARCH:	PRE-ECLAMP$4.TI.	[EMED]
	26. SEARCH:	(PRE ADJ ECLAMP$4).TI.	[EMED]
	27. SEARCH:	PREECLAMPSIA.W..MJ.	[EMED]
	28. SEARCH:	24 OR 25 OR 26 OR 27	[EMED]
	29. SEARCH:	23 OR 28	[EMED]
	30. SEARCH:	PREGNAN$5.TI,AB.	[EMED]
	31. SEARCH:	PREGNANCY.W..MJ.	[EMED]
	32. SEARCH:	30 OR 31	[EMED]
	33. SEARCH:	29 AND 32	[EMED]
	34. SEARCH:	33 AND LG=EN	[EMED]
	35. SEARCH:	34 AND REVIEW=YES	[EMED]
	36. SEARCH:	34 AND PT=META-ANALYSIS	[EMED]
	37. SEARCH:	34 AND (CLINICAL-TRIALS# OR PT=CLINICAL-TRIAL#)	[EMED]
	38. SEARCH:	35 OR 36 OR 37	[EMED]

APPENDIX 2: PROFORMA FOR CHAPTER 3

ABPM PROFORMA

NUMBER						CASE NO:		
DOB	G P +	AGE	RACE	CIGS/D	ALC/W	HT	WT	BMI
PREVIOUS HISTORY:								
CHILD DOB 1.	GEST	W	M	PIH Y/N	PET Y/N	MEDICAL PROBLEMS 1.	BP PRE PREG	
2.				Y/N	Y/N	2.	DRUGS AT CONCEPTN	
3.				Y/N	Y/N	3.	METANEPH	
4.				Y/N	Y/N	4.	IVP	USS
INDEX PREGNANCY:								
LMP / /				EDD / / US/MP		BOOKING BP / @ /40		BOOKING URINE ALB/BLD/GLU

LOC	DAT	G	BP	PR	PR24	PL	UA	ALT	ALB	DRUGS

DU ATTENDANCES	ABPM MEAN: 1 / /	2 / /	3 / /
NO OF ADMISSIONS FOR BP		TOTAL DAYS INPATIENT	

DATE ADMITTED	GESTATION	STAY (DAYS)	NOTES
1			
2			
3			
4			
5			
6			
7			

OUTCOMES

IUGR Y / N / /	ABSENT EDF Y / N / /	REVERSE EDF Y /N / /	OLIGO Y / N / /

ECLAMPSIA Y / N / /	DIC Y / N	MAG Y / N	HDU Y / N NO OF DAYS:	

LABOUR:

IOL: Y / N	DOB / /	GESTATION	MODE	INDICATION

BABY DATA:

APGAR	1	5	WEIGHT (G)	SEX M / F	ALIVE Y / N	NNU: Y / N STAY:

POSTNATAL:

6 WKS P/N BP:	DRUGS AT 6 WKS	FURTHER INFO

APPENDIX 3: POSTER FOR TRIAL

ABPM TRIAL STARTS ON MARCH 11, 2002!

Who is eligible?

- Pregnant women aged 16 or over: outpatients or inpatients
- Diastolic BP of 90 mmHg or more (two readings at least 4 hours apart)
- No history of diabetes or renal disease
- Not needing delivery in the next 24 hours

Why are we doing the study?

- Ambulatory blood pressure monitoring (ABPM) may give a better assessment of BP. This might decrease unnecessary interventions and may also identify women at higher risk of poor outcomes.

What is the study design?

- All women will have ABPM. Half will be randomized to revealing the results to the Obstetric team and half will have results concealed.

What do I do?

- Find the purple file in ANC, on the day unit or on wards 4 & 5
- Give out the patient information leaflet and answer questions
- If declines, record patient details and reason
- If agrees, contact Cathy Rhodes to consent the woman for the study
- Contact the Day Unit to organise ABPM
- Put purple sticker on outside of hospital notes
- For every woman put in the study and for any queries, contact:

Cathy Rhodes, research fellow for ABPM trial

[Bleep]/[Phone]

THANK YOU VERY MUCH FOR HELPING WITH THIS STUDY!

APPENDIX 4: DAY UNIT STAFF: DETAILED

INSTRUCTIONS FOR ABPM TRIAL PATIENTS

Patient is eligible if:

- Any stage of pregnancy, diastolic BP 90 mmHg or more on two readings at least 4 hours apart
- Never had ABPM
- Over 16 years old and no diabetes/renal disease
- Doesn't need delivery in next 24 hours

Give information sheet (patient to keep this) and answer questions. If doesn't agree to take part, record name, hospital number and reason for declining.

If agrees to take part:

- Inform Dr C Rhodes (research fellow) to complete 3 consent forms: one each to patient, hospital notes and trial records
- Allocate patient identification number (PIN) for the trial
- Note in trial log the date, PIN, name, hospital number, and consultant
- Put trial sticker on hospital and hand-held notes
- Arrange ABPM, ideally immediately

GROUP A (REVEALED):

- Dr Rhodes will give ABPM results and letter to consultant
- ABPM results to be filed in notes to ensure this is seen by all; one copy to research fellow
- Can have ABPM again if clinicians wish, organise as normal.

GROUP B (CONCEALED):

- Dr Rhodes will contact Consultant by letter to inform
- Results are kept where no-one will have access.
- Care continues as normal but not to have ABPM again during pregnancy.

APPENDIX 5: PATIENT INFORMATION SHEET

PATIENT INFORMATION SHEET

1. Title of study

'A randomized comparison of ambulatory blood pressure monitoring versus conventional office blood pressure measurement in the management of pregnant hypertensive women'

2. Invitation to take part

You are being invited to take part in a research study to test a new method of measuring blood pressure in pregnant hypertensive women, which means women with high blood pressure in pregnancy. Before you decide it is important that you understand why the research is done and what it involves. Please read this sheet carefully. Do ask us if anything is not clear or if you want to know more. Thank you for reading this.

3. What is the study about?

Good Hope Hospital wants to try to improve care for pregnant women suffering from high blood pressure. High blood pressure affects about one in ten of all pregnant women. They are seen more often in clinics and have more admissions to hospital. Some of these women may not have high blood pressure at home or under normal conditions and do not need this extra care.

Women who truly have high blood pressure can be admitted to hospital for long periods. A better way of assessing their blood pressure and the risk to them and their baby would be helpful. This might mean less time in hospital for these women.

4. **What new technique is being studied?**

The new technique we are looking at is called **Ambulatory Blood Pressure Monitoring.** Ambulatory blood pressure monitors are worn on a belt or shoulder strap like a portable tape recorder. They automatically measure blood pressure while a woman is at home or work during her daily routine, or up and about in hospital. This can give a more realistic record of blood pressure. Care in pregnancy may be improved, based on these results.

This method of measuring blood pressure may lead to less interference in the pregnancies of some women. This could reduce the number of procedures such as caesarean sections or induction of labour (starting labour off using drugs or 'breaking the waters'). In order to test this idea, we are doing a research study of ambulatory blood pressure monitoring in pregnancy.

5. **Why have I been chosen?**

You have been chosen because your blood pressure measurement is raised. If your hospital doctor thinks you need to be treated for high blood pressure and delivered in the next 24 hours you will not take part in the study.

6. **Do I have to take part?**

It is up to you to decide. If you do not want to take part your doctors and midwives will manage you in the usual way. It will **not** affect the quality of care you will receive.

7. What will happen to me if I take part?

You will have 24 hours of blood pressure monitoring using the ambulatory monitors. As we don't yet know which way of measuring blood pressure is best, we need to make comparisons between the current standard blood pressure measurement and the use of the new technique. We will do this by dividing women taking part into two groups.

For one group, the doctor **will** be given the results of the patient's ambulatory blood pressure recording, which he or she can then use in planning the patient's care. For the second group, the doctor **will not** be given the results of the patient's ambulatory blood pressure recording. In this second group of women, the doctor will only have the clinic blood pressure readings to use in planning the patient's care. This is the current way of making a blood pressure assessment.

After you have had your baby, you will be sent a short questionnaire at home. This is so we can get your views about the monitoring. As you are the person undergoing the monitoring it is very important for us to have your opinions.

8. How will you decide which group I will be in?

Which group you are in will be decided by chance, like the toss of a coin, so you will not be able to choose a particular group. At the end of the study the results will be analysed to see if the new technique does save women from extra interference during their pregnancy.

9. What are the benefits and risks?

The reason for the study is to see if the technique is helpful. As yet we do not know if it is. We only think that it may be. The risks are very few. The monitors themselves sometimes cause discomfort in the arm when the cuff is blown up to take a measurement. If this becomes too uncomfortable then the cuff can be removed.

Your doctors will have all the usual information from the clinic and ward blood pressures to look after you. For half of the women entered into the study the hospital doctor will have the extra information from the monitoring to base decisions on. Any change in your care will be based on extra information and not less.

You may have a worryingly high blood pressure on the ambulatory blood pressure monitoring and be in the group where results are not given to your doctor. If this happens you will be taken out of the study and the results of the monitoring will be sent to your hospital doctor.

10. What happens to the information?

Your notes and your baby's notes will be reviewed as part of the study. The information collected for the study will be held in one place. Only your hospital number will identify you. All the information will be absolutely confidential and not released to anyone else. When the study and its written reports are complete the information will be destroyed. If you wish to see your own information at any time this can be sent to you when you ask for it in writing. At the end of the study written reports will be sent for publication in the scientific medical press. Summary copies will be made available to you if you request them.

11. **What if something goes wrong?**

If something goes wrong your right to compensation is not affected. You may make any complaints in the usual manner through the NHS complaints procedure.

12. What happens now if I decide to take part?

If you do decide to take part in the study we will ask you to sign a consent form.

Arrangements will then be made for you to have the ambulatory blood pressure monitoring.

You will be given a copy of this sheet and a signed consent form to keep.

13. What happens if I change my mind?

You can change your mind at any time and withdraw from the study. It will not affect your care at all, which will carry on in the same way as before the study. All women will receive the highest standard of care possible at all times.

14. What if I have more questions?

If you have more questions then please contact Dr Rhodes, research fellow with Mr D Churchill at Good Hope Hospital.

Contacts and telephone numbers

Research Fellow at Good Hope Hospital:

Dr Cathy Rhodes

Telephone: 0121 378 2211 Ext: 3084, or ask switchboard to page Dr Rhodes

If you are able to co-operate with this study your help would be most appreciated. Thank you for taking time to read this and consider being in the study.

Date information sheet completed: 30/8/02 (Version 2)

APPENDIX 6: PATIENT CONSENT FORM

Patient Identification Number for this trial:

CONSENT FORM

A RANDOMIZED COMPARISON OF AMBULATORY BLOOD PRESSURE MONITORING VERSUS CONVENTIONAL OFFICE BLOOD PRESSURE MEASUREMENT IN THE MANAGEMENT OF PREGNANT HYPERTENSIVE WOMEN

Please initial box

1. I confirm that I have read and understand the information sheet dated 30/08/02 for the above study and have had the chance to ask questions. ☐

2. I understand that my taking part is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of my and my baby's medical notes may be looked at by medical, midwifery and regulatory authority staff where it is relevant to my taking part in research. I give permission for these individuals to have access to these records. ☐

4. I agree to take part in the above study. ☐

Name of patient	Date	Signature
Name of person taking consent (if not researcher)	Date	Signature
Researcher	Date	Signature

A signed copy each to patient, researcher and hospital notes.

APPENDIX 7: CONSULTANT LETTERS

date

Dear

Name no

The above patient consented to be in the ambulatory blood pressure monitoring study. She was allocated to Group A, where her result is revealed. The result is enclosed for your information and to be filed with this letter in her hospital notes. If you wish her to have further ABPM recordings these would be arranged in the usual way and the results filed in her notes routinely.

Thank you very much for your help.

Yours sincerely,

Dr Cathy Rhodes MRCOG

Research Fellow

Date

Dear

Name **Reg No**

The above patient consented to be in the ambulatory blood pressure monitoring study. She was randomized to Group B, where her result is concealed. Please file this letter in the hospital notes.

Thank you very much for your help.

Yours sincerely,

Dr Cathy Rhodes MRCOG

Research Fellow

APPENDIX 8: PROFORMA FOR CHAPTER 4

ABPM TRIAL PROFORMA CASE NO:

NUMBER		HOSPITAL		DOB	AGE	ETH
GRAV	PARITY	HT	WT	BMI	CIGS/D	CON

PREVIOUS HISTORY:						**MEDICAL PROBLEMS**	
CHILD DOB 1.	GEST	W	M	PIH Y/N	PET Y/N	1.	DRUGS AT CONCEPTN
2.				Y/N	Y/N	2.	
3.				Y/N	Y/N	3.	BOOKING BP
4.				Y/N	Y/N	4.	GESTATION BOOKED

INDEX PREGNANCY:		**No of fetuses: 1 / 2**	
LMP / /	EDD / /	BASIS EDD USS / LMP / BOTH	BOOKING URINE ALB/BLD/GLU
MARK TRIAL ENTRY WITH A 'T'		**GROUP ALLOCATION: A / B**	

LOC	DAT	G	BP	PR	PR24	PL	UA	ALT	ALB	DRUGS/SX/ NOTES

LOC	DAT	G	BP	PR	PR24	PL	UA	ALT	ALB	DRUGS/SX/ NOTES

NO OF COMMUNITY CLINIC ATTENDANCES

WERE EXTRA CMW VISITS NEEDED FOR BP CHECKS? Y / N

DU ATTENDANCES	ABPM MEAN: 1 / /	2 / /	3 / /
NO OF ADMISSIONS FOR BP:		TOTAL DAYS INPATIENT:	

DATE ADM	DATE DISCH	STAY	GEST	NOTES: REASON FOR ADMISSION BLOODS/MAX BP/UR/SX/DRUGS
1				
2				
3				
4				

OUTCOMES						
IUGR Y / N / /		ABSENT EDF Y / N / /		REVERSE EDF Y /N / /		OLIGO Y / N / /
ECLAMPSIA Y / N / /		ABRUPT Y / N	DIC Y / N	MAG Y / N	RENAL Y / N	HDU Y / N NO OF DAYS:
PPH Y / N		TRANSFN Y / N		INFECTN Y / N		
LABOUR:				ANALGESIA: NIL/NO/PETH/EPID/SPIN		
IOL: Y / N	INDICN	METHOD	DOB / /	GEST	MODE	INDICATION
BABY DATA:						
APGAR Baby 1 Baby 2	1	5	WEIGHT (G)	HC	LENGTH	SEX M / F
ABG: pH BE Baby 1 Baby 2			VBG: pH BE Baby 1 Baby 2	ALIVE	NNU: 1 2 Y/N: STAY: ITU: NNU:	VENT:1 2 Y/N: DAYS:
COMPLICATIONS: RDS / NEC / IVH / NEONATAL DEATH						
DATE MOTHER DISCHARGED / / DRUGS @ DISCHARGE				DATE BABY DISCHARGED Baby 1: / / Baby 2: / /		
POSTNATAL: HOSPITAL / GP						
6 WKS P/N BP:		DRUGS AT 6 WKS		FURTHER INFO		

APPENDIX 9: PATIENT QUESTIONNAIRE & LETTER

Date:

Dear

I am writing to thank you again for agreeing to take part in the study on 24-hour ambulatory blood pressure monitoring in pregnancy at Good Hope Hospital. Your contribution to this research work is greatly appreciated.

We feel it is important that we assess your experience of the monitoring. To do this, we would be very grateful if you would take a few minutes to complete the questionnaire enclosed with this letter. A stamped addressed envelope is enclosed for your reply.

Thank you again for your help.

Yours sincerely,

Dr Cathy Rhodes MRCOG
Research Fellow to Mr Churchill

AMBULATORY BLOOD PRESSURE MONITORING QUESTIONNAIRE

PIN:

Please circle one answer for each question.

1. How was the use of your arm while wearing the blood pressure cuff?
   No limits to use / Slightly limited / Moderately limited / Severely limited

2. How did the blood pressure cuff feel on your arm?
   No discomfort / Slight discomfort / Moderate discomfort / Severe discomfort

3. Could you perform normal daily activities during the monitoring?
   No limits to activities / Slightly limited / Moderately limited / Severely limited

4. Did the noise of the monitor disturb you?
   No / Slightly / Moderately / Severely

5. How was your sleep pattern during monitoring?
   Not disturbed / Slightly disturbed / Moderately disturbed / Severely disturbed

6. If 24-hour blood pressure monitoring became a part of routine pregnancy care, would you be willing to have it again in a future pregnancy?
   Yes / No

PLEASE USE THE SPACE BELOW TO ADD ANY FURTHER COMMENTS:

Thank you for completing this questionnaire. Please return it in the stamped addressed envelope.

APPENDIX 10: ETHICAL APPROVAL

See next two pages.

APPENDIX 11: CONSORT STATEMENT 2001 CHECKLIST:
ITEMS TO INCLUDE WHEN REPORTING A RANDOMIZED TRIAL.

PAPER SECTION **And topic**	**ITEM**	**Descriptor**	**Reported on Page #**
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned").	Title p 126 Abstract p 127
INTRODUCTION Background	2	Scientific background and explanation of rationale.	Background in Introduction p 128 Also refers to Section 1.4
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	Participants p 128 onwards: Inclusion & exclusion criteria, setting
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	Intervention p 129 onwards, full details
Objectives	5	Specific objectives and hypotheses.	Hypothesis and objective described p 127 (Abstract), p 128 (Background)
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	Outcome measures in Table 4.1 (p 133)
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	Power calculations in Table 4.2 (p 136)
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)	Described in randomization section (p 129 on)
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	Described in randomization section (p 129 on), was concealed until intervention assigned.
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	Described in randomization section (p 129 on)
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	Described in randomization section (p 129 on). All blinded until intervention complete as per protocol.
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	In statistics section p 135. One subgroup analysis: overall induction of labour.

PAPER SECTION **And topic**	**ITEM**	**Descriptor**	**Reported on Page #**
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	Figure 4.2 (p 138) shows flow diagram of participants through trial. Text p 137, no protocol violations.
Recruitment	14	Dates defining the periods of recruitment and follow-up.	Results: p 137 for recruitment dates. Outcome measures ended at delivery. 6 week follow up attempted but poor attendance (p 142)
Baseline data	15	Baseline demographic and clinical characteristics of each group.	Table 4.3 p 139
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).	All tables include number in denominator, absolute numbers given, page 136 stated 'intention-to treat'.
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval).	Tables 4.4, 4.5, 4.6 summarise groups separately, effect size with confidence intervals.
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	Overall inductions analysed (not prespecified). No other analyses.
Adverse events	19	All important adverse events or side effects in each intervention group.	Nil occurred. Results: p 137
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	Multiplicity p 145. Discussion includes induction including hypothesis. Limitations of study discussed.
Generalizability	21	Generalizability (external validity) of the trial findings.	In Statistics section p 135 Discussion p 148 mentioned issues of local staff familiarity with the technique
Overall evidence	22	General interpretation of the results in the context of current evidence.	In Discussion especially related to studies in chronic hypertension p 151

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