W.H. BIRKENHÄGER and J.L. REID

HANDBOOK OF HYPERTENSION

Volume 21

HYPERTENSION IN PREGNANCY

Editor: P.C. Rubin

ELSEVIER

Handbook of Hypertension

Series Editors: W.H. BIRKENHÄGER and J.L. REID

VOLUME 21

Hypertension in Pregnancy

Editor:

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University of Nottingham,
Nottingham, UK

2000
ELSEVIER
Amsterdam – Lausanne – New York – Oxford – Shannon – Singapore – Tokyo

ELSEVIER SCIENCE B.V.
Sara Burgerhartstraat 25
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

ISBN: 0 444 50416 8 (Vol. 21)

ISBN: 0 444 90341 0 (Series)

♾ The paper used in this publication meets the requirements of ANSI/ISO Z39.48-1992 (Permanence of Paper).
Printed in The Netherlands

Hypertension in Pregnancy

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Foreword

The format of the *Handbook of Hypertension* was conceived in the late 1970s, when it had become clear that the trunk of hypertension research sprouted a rapidly increasing number of branches, some of which showed faster growth rates than others. Consequently we attempted to conform the organization of the Handbook to these dynamics, through generating specific volumes instead of a tome covering the entire domain. We envisaged that this procedure would not only prevent a waste of paper, but also provide a measure of flexibility in the matter of meeting the need for updating topics in relation to their scientific turnover rates. Over the years, this has proven to be a viable option, even though it was not always possible to keep pace with the speed of developments. So far the diligence of our Volume Editors has enabled us to replace Volumes 1 and 2 with No. 15 (Clinical Hypertension), Volume 4 with No. 16 (Experimental and Genetic Models of Hypertension), Volume 5 with No. 11 (Clinical Pharmacology of Antihypertensive Drugs), Volume 6 with No. 20 (Epidemiology of Hypertension), and Volumes 7 and 8 with No. 17 (Pathophysiology of Hypertension). Down the road we have adapted the referencing to the Vancouver Style, with an additional measure of mentioning all authors in quoted papers. This, at least to us, seems to be not only a relevant source of information, but also a simple matter of courtesy to those who provide the base of our accumulated knowledge.

On the present occasion we take pleasure in presenting the update of former Volume 10 (Hypertension in Pregnancy), again coordinated by Professor P.C. Rubin as Volume Editor. This edition exhibits the scientific progress achieved with regard to the multifactorial fabric of (pre-)eclampsia, wherein pregnancy-induced hypertension now appears to become just one of the many facets of the syndrome. The potential therapeutic implications of this systematic disorder are still under investigation, but one may assume that the reader's interest in such further developments will be stimulated by the present intriguing display of the many mechanisms involved in its pathophysiology.

Other earlier volumes are also in the process of revision. The volumes on Pharmacology of Antihypertensive Drugs (Vol. 3) and Clinical Pharmacology of Antihypertensive Drugs (Vols. 5 and 11) will now be integrated into a new concept entitled Pharmacology and Therapeutics of Hypertension. The topic of Hypertension in the Elderly (Vol. 12), one of the important clinical hypertension topics of today, will be a further candidate for thorough revision. In the same vein, we have planned an update on Blood Pressure Measurement, a subject which has recently come of age through the rapidly growing expertise with ambulatory blood pressure monitoring (ABPM).

By necessity the addition of new volumes will have to proceed at a slower pace,

given the already wide coverage in this series. One long-awaited project will be a scientifically based historical account to be entitled 'XXth Century Hypertension Research'. This volume is intended to bridge the increasing gap in the awareness of the younger generations (investigators and clinicians alike) with regard to the breakthroughs achieved particularly in the second half of the 20th Century.

After that, we hope to reflect the present great leap forward in hypertension research by issuing a volume entitled 'Molecular Genetics and Pharmacogenomics of Hypertension'. In the new Millenium we wish to encourage the increasing interaction with both the Volume Editors and the Authors, as well as the Readership of the Handbook Series, from whom any suggestions for further exploration in the series will be welcomed and carefully considered.

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Preface

Just before Christmas 1953 a 25-year-old woman was admitted to Glasgow Royal Maternity Hospital for induction at the 38th week of gestation. Earlier in the pregnancy her blood pressure had been 120/70 mmHg, but now it was 160/130 and had not responded to bedrest. The delivery was uneventful and the patient transferred to the postnatal ward: 17 h later she had a generalized convulsion lasting 3 min. The patient was transferred to the labor ward, unconscious and cyanosed. She was given oxygen and a quarter grain of morphia, followed by paraldehyde. No further seizures occurred and the blood pressure was returning towards normal by the time of her discharge 10 days later.

Just before Christmas 1985 this patient's daughter was admitted convulsing to the Queen Mother's Hospital in Glasgow. She was at the 34th week of gestation. Earlier in the pregnancy her blood pressure had been 114/60 mmHg, but now it was 165/120. She had been apparently normal until that morning when she went to have a bath. Her husband (who would normally have left for work at this time of day) heard a strange noise from the bathroom and found his wife convulsing under water. On arrival at the hospital the seizures were controlled with diazepam and further seizures prevented with phenytoin. The blood pressure was returned towards normal by an infusion of hydralazine and cesarian section produced a healthy infant. Both mother and baby did well, the blood pressure returning to normal by the 3rd postnatal month. CT scan and immunological screening were normal.

Over the more than 30 years which separated these events, fashions in treatment have changed, the range of investigations has become more sophisticated, but the enigma of eclampsia is just the same. What is it that makes apparently normal young women so ill as to be at risk of death? To all those who ask this question I believe this book will be of interest.

The big breakthrough has not yet happened: we still do not know the cause of pre-eclampsia and in that regard this fascinating condition is the same enigma that it was when the first edition was prepared more than 10 years ago. Nonetheless, pieces are being put into the jigsaw puzzle and several groups are defining more clearly the mechanisms and inheritance of pre-eclampsia.

Nor have there been any great new treatments, but clarification has been available in plentiful supply. Aspirin did not fulfill its early promise but at least the hypothesis that it would prevent pre-eclampsia was properly tested in a large clinical trial. Another big trial showed that magnesium was better than diazepam or phenytoin in the secondary prevention of eclampsia, although many thought they knew that on the basis of half a century of clinical experience.

This book, like its predecessor, draws specialists from around the world to provide a detailed reference source of hypertension in pregnancy. It covers a range of topics from basic science to clinical practice and will, I hope, provide a useful basis for readers to learn about this important and intriguing subject.

I would like to express my thanks to my PA, Louise Sabir, who has contributed much to the organization of this second edition.

PETER C. RUBIN

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P.C. Rubin, editor

1. Cardiovascular physiology in normal pregnancy

Michael de Swiet

I. INTRODUCTION

For many years thinking about the cardiovascular system in pregnancy has been dominated by changes in cardiac output, in particular the timing in gestation of any pregnancy induced change and its magnitude. With regard to the stimulus to change, attention was focused on mechanisms increasing cardiac contractility such as high oestrogen levels or increasing pre-load such as increased circulating blood volume. But more recently it has been realized that the most likely cause of increased cardiac output is a decrease in after load, i.e. vasodilatation occurring before any other changes in the circulation (1). This in turn could cause the well known mid-trimester fall in systemic arterial pressure. In addition failure of vasodilatation is a recognized correlate of pregnancy failure due to pre-eclampsia or intrauterine growth restriction, both of which have their antecedents in placental development in very early pregnancy.

Unfortunately it is impossible to measure peripheral arterial resistance directly though analysis of Doppler blood flow patterns by Laplace transformation may derive indices that relate to peripheral resistance (2). Therefore changes in arterial resistance e.g. vasodilatation still have to be inferred from changes in the relation between cardiac output and perfusion pressure.

II. BLOOD PRESSURE

Systemic arterial pressure

General errors in the measurement of blood pressure and those that are specific to pregnancy are considered elsewhere in this book. They contribute to the weakness of

data relating to population studies of blood pressure change in pregnancy. In addition there is the problem that if the blood pressure rises in pregnancy, it is considered to be pathological, i.e. due to pre-eclampsia or some variant of the condition, rather than physiological. Thus subjects whose blood pressure rise in the second half of pregnancy over some arbitrary level tend to be treated as pathological and get excluded from physiological studies.

Within these constraints the same general pattern of blood pressure change has been found by most observers, i.e. relatively little change in systolic pressure, but a marked fall in diastolic pressure, which is lowest at mid-pregnancy and which rises thereafter to approximately non-pregnant levels by term, so that for much of pregnancy there is a notably raised pulse pressure (see Fig. 1 and references (3,4)). The description is representative rather than numerical because the actual readings, which vary considerably from study to study, are influenced by the techniques of measuring blood pressure. Absolute levels are also influenced by other factors, such as age and the time of day.

A considerable modification which has been extensively studied is that due to posture. The effect of posture on arterial blood pressure is by no means decided, and differences of opinion are well illustrated by the contrasting studies of Schwarz (4) and MacGillivray et al. (3). Schwarz described a fall in both systolic and diastolic pressure when the subject moved from sitting to lying, whereas MacGillivray found a marked rise in systolic pressure but essentially no change in diastolic pressure (Fig. 1).

Occasionally there may be a profound fall in blood pressure in a pregnant woman lying on her back: the supine hypotensive syndrome, About 10% of women may have a fall of at least 30 mmHg in systolic blood pressure after lying on their backs for 3–7 min, and in some the fall may be so profound as to resemble surgical shock (5). Fainting in this condition has been shown to relate to reduced cerebral blood flow (6): the fetus may also be affected (7) presumably by impaired maternal uterine blood flow. The phenomenon is thought to be due to compression of the vena cava by the uterus though the fetus may also be affected by compression of the aorta (8).

An important methodological error contributes to the apparent fall in blood pressure when patients turn from lying supine to lying on their side. In order to measure blood pressure consistently, the sphygmomanometer cuff should be at a constant reference level relative to the heart: usually the level of the left atrium is chosen. When patients turn from lying supine to lying on one side, the arm is usually kept beside the body, and is thus raised about 10 cm relative to the heart if the arm is uppermost. This alone would account for an apparent fall in blood pressure of 10 cm of blood or about 7 mmHg. In several studies (9,10) this factor alone accounted for all the effect of rolling over from supine to the left lateral position. It may also account for some of the variability in the effect of changing posture from sitting to lying already referred to.

There is a further rise in blood pressure during labour. In a study of 15 women in labour and therefore given analgesics, Robson et al. (11) showed that mean blood pressure rose from 82 to 84 mmHg at the beginning of labour with a further rise in basal mean blood pressure to 91 mmHg at the end of the first stage. Measurements were made in the left lateral position. Uterine contractions were associated with rises in mean blood pressure of about 10 mmHg paralleling the changes in cardiac output during labour commented on below.

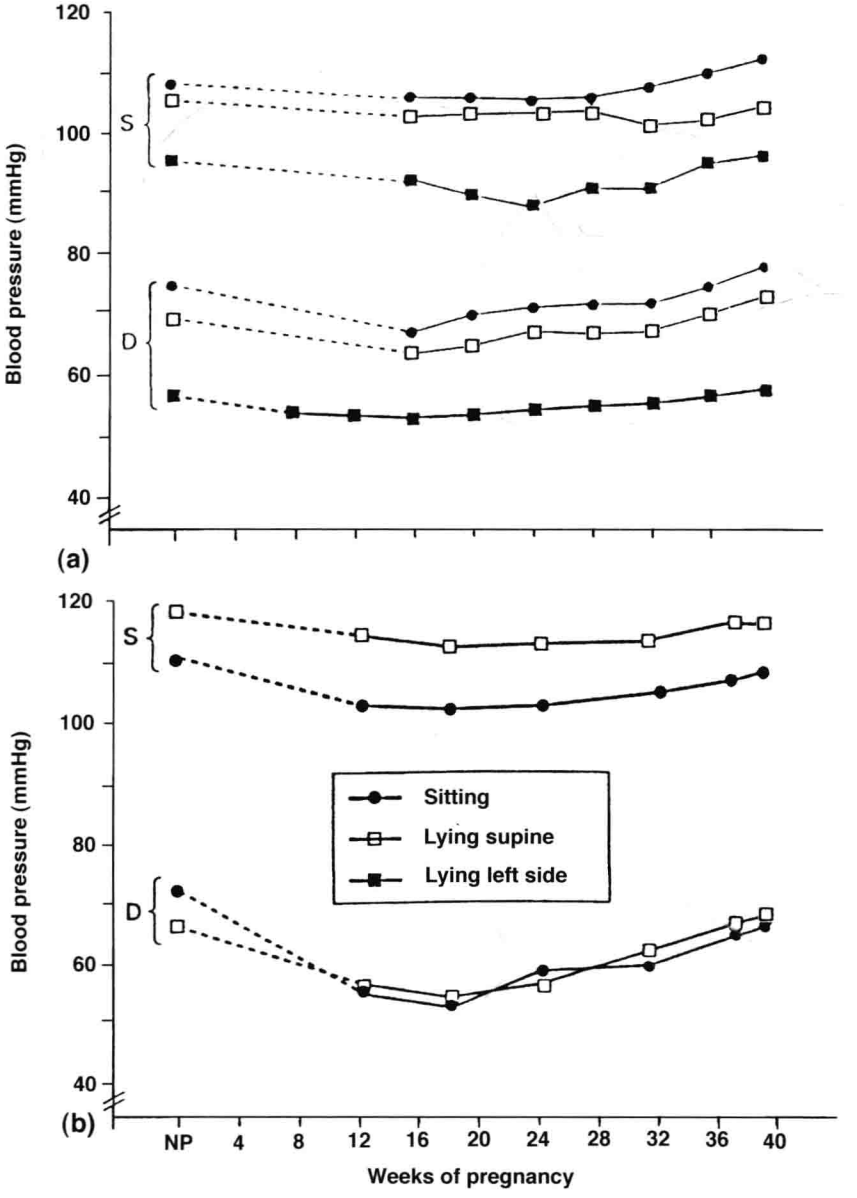

Fig. 1. Effect of pregnancy on postural blood pressure, systolic (S) and diastolic as found by (a) Schwarz (4) and (b) MacGillivray et al. (3). Note that MacGillivray finds sitting blood pressure consistently lower than the supine, whereas Schwarz finds the opposite.

Ambulatory blood pressure measurement

The process of conventional sphygmomanometry is such that only isolated measure-

ments can be made. While such measurements are appropriate for assessment of the circulation at a single point in time (and this, in itself, may be very valuable), they do not give a representative picture of overall blood pressure change during pregnancy: in part because of the inherent variability of blood pressure, both random and diurnal, and also because of extra variability induced by the circumstances of blood pressure measurement.

There have been a few studies of continuous intra-arterial blood pressure measurement in pregnancy (12) but this is such an invasive technique that very few subjects have been studied in this way, certainly not enough to give reliable longitudinal data for the effect of pregnancy on blood pressure. It is unlikely that further continuous intra-arterial studies will be sanctioned because of the development of relatively small portable devices which can be programmed to inflate a sphygmomanometer cuff and then use a detection system (either auscultatory or oscillometric) to record blood pressure.

The data are usually recorded in machine-readable form and may be down-loaded for further analysis. These instruments were first applied to the assessment of hypertension in non-pregnant individuals; at least 40 different systems are available. The majority of these instruments have not been adequately validated by the criteria of the Association for the Advancement of Medical Instrumentation (AAMI) (13) or the British Hypertension Society (14) to ensure accuracy and reliability of measurement in the non-pregnant state. But because of the change in haemodynamic pattern of pregnancy and further change in vascular characteristics induced by pre-eclampsia, such instruments should be specifically validated in normal and pre-eclamptic pregnancies (15) if they are to be used in such circumstances.

Halligan et al. (16) used the Space-Labs 90207 ambulatory system which has been validated in pregnancy (17) and in pre-eclampsia (18) to study 24-h ambulatory blood pressure in 106 primgravidae. As in the non-pregnant state, ambulatory blood pressures were lower than office blood pressures and by about 7 mmHg in pregnancy. There was a marked fall at night of about 15 mmHg in both systolic and diastolic blood pressure. Ambulatory blood pressures do fall in pregnancy but the effect was not nearly so marked as noted in the study of MacGillivray et al. (3) (see Fig. 1) and the nadir was spread over wider gestational ages, 9–24 weeks. Interestingly, Halligan et al. (16) also found a different pattern of office blood pressure response to pregnancy with nadirs in systolic and diastolic blood pressure occurring at 33–40 weeks.

Pulmonary blood pressure

Angelino et al. (19) and Bader et al. (20) using cardiac catheterization showed that pressure in the right ventricle, the pulmonary artery and the pulmonary capillaries remained at the normal non-pregnant level throughout pregnancy. This would be expected since the pulmonary circulation is known to have a great capacity for absorbing high rates of blood flow without pressure change. It can do this only by decreasing resistance to flow, probably by dilatation of the vascular bed, so that when cardiac output is increased, the volume of the pulmonary circuit also increases. The characteristic radiographic appearance of increased vascularity and enlarged pulmonary vessels supports this view.

Pulsed Doppler pulmonary blood velocities may be used to calculate pulmonary