# POSTURAL BLOOD PRESSURE DIFFERENCES IN PREGNANCY

A study of blood pressure differences between supine and left lateral positions as measured by ultrasound

**P. W. J. VAN DONGEN**

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**PROEFSCHRIFT**

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE KATHOLIEKE UNIVERSITEIT TE NIJMEGEN, OP GEZAG VAN DE RECTOR MAGNIFICUS PROF DR P G A B WIJDEVELD, VOLGENS BESLUIT VAN HET COLLEGE VAN DECANEN IN HET OPENBAAR TE VERDEDIGEN OP DONDERDAG 7 JUNI 1979 DES NAMIDDAGS TE 2.00 UUR PRECIES

door

**Pieter Willem Jozef van Dongen**

geboren te Dongen

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*Opgedragen aan Loes en*

*onze vier zonen*

Het onderzoek naar de verschillen in bloeddruk bij zwangeren in rug- en zijligging werd verricht in de kliniek en polikliniek van de afdeling obstetrie en gynaecologie in het St.Radboud-ziekenhuis, Nijmegen.

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P.W.J. van Dongen

| | |
|---|---|
| ADBP | average diastolic blood pressure |
| AMBP | average mean arterial blood pressure |
| ASBP | average systolic blood pressure |
| AII | angiotensin II |
| Basal blood pressure | blood pressure measured under standardized conditions which eliminate emotional and physical stimuli (ultrasound method) |
| BP | blood pressure = systemic arterial blood pressure (in mmHg) |
| Casual blood pressure | blood pressure measured without standardized conditions (auscultatory method) |
| CO | cardiac output |
| C.s. | caesarean section |
| $\Delta$(S,D,M,P) | postural difference in blood pressure between the supine and left lateral positions (systolic,diastolic,mean arterial and pulse pressures) |
| $\bar{\Delta}$ | average $\Delta$ |
| DBP | diastolic blood pressure |
| Direct method of blood pressure measurement | invasive method of blood pressure measurement |
| Df | degree of freedom |
| DS | dehydroisoandrosterone sulfate |
| F | female |
| Gest. | gestation |
| HCG | human chorionic gonadotropin |
| HMG | human menopausal gonadotropin |
| Ht | height |
| HT | hypertension |
| Indirect method of blood pressure measurement | non-invasive method of blood pressure measurement |
| M | male |
| MAP | mean arterial pressure |
| MAP 2 | MAP in the second trimester of pregnancy |
| MAP 3 | MAP in the third trimester of pregnancy |

| | |
|---|---|
| MCR | metabolic clearance rate = volume of plasma completely cleared of a substance per unit time |
| mmHg | millimeters of mercury |
| Neg.disc. | negative discongruency |
| NS | not significant |
| p | probability |
| %ile | percentile |
| PGE | prostaglandins of the E-series |
| PHT | pre-existing hypertension |
| PIFG | poor intrauterine foetal growth |
| PIH | pregnancy induced hypertension |
| PNM | perinatal mortality |
| Pos.disc. | positive discongruency |
| Positional BP difference | postural difference in blood pressure |
| Postural BP difference | the difference of the blood pressures between the supine and left lateral positions (=Δ) |
| p.p. | post partum |
| Q.I. | Quetelet's Index |
| r | correlation coefficient |
| R | peripheral vascular resistance |
| RAA | renin-angiotensin-aldosterone |
| Resting blood pressure | basal blood pressure |
| RR | Riva-Rocci: the auscultatory blood pressure measurement according to the principles described by Riva-Rocci and Korotkow |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SGA | small-for-gestational age |
| SHS | supine hypotensive syndrome |
| Sq | square |
| Wt | weight |

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Hypertension is frequently discovered during the course of pregnancy. Pregnancy induced hypertension may be considered to be a condition which develops without pre-existing hypertension, and disappears after the early post partum period. Pre-existing hypertension often becomes aggravated during pregnancy. Hypertension may be one symptom of the known triad of (pre-eclamptic) toxaemia: oedema (weight gain), proteinuria and hypertension.

Growth retardation of the foetus, as a consequence of placental insufficiency, is often one of the sequelae of hypertension in pregnancy. This placental inadequacy can eventually lead to intrauterine foetal death. Small-for-dates infants are at high risk for enhanced mortality and morbidity during and after the neonatal period. Overall perinatal mortality increases when the diastolic blood pressure exceeds 90 mmHg. It is rarely specified in the literature, however, in what position these blood pressures have been measured.

The postures in which the blood pressures are measured influence greatly the observed blood pressure levels. Higher blood pressures are found in standing and sitting positions as compared with the supine recumbent position. In addition, differences in blood pressure have been found between supine and lateral recumbency. This is true for both pregnant and non-pregnant subjects.

It has been suggested that some pregnant nulliparous women between the 28th and the 32nd week of pregnancy show an exaggerated postural blood pressure response when "rolled-over" from the left lateral to the supine position. Those who developed later in pregnancy the so-called pregnancy induced hypertension were said to show an increase in the diastolic blood pressure of more than 20 mmHg in the supine postion as compared with the control, left lateral blood pressure.

Many endogenous and exogenous factors influence the blood

pressure levels in pregnant women. Some subjects react to "pressor substances" more readily than others. Thegravid uterus will compress the inferior vena cava after the 28th week of pregnancy when the subject is lying on her back. Thus, many haemodynamic changes occur when the pregnant woman in late pregnancy turns from the lateral to the supine position. The possibility was therefore considered that some gravidae might overreact to these haemodynamic alterations , and, further, that an exaggerated systemic blood pressure response might indicate those women with hyperreactive uteroplacental vascular beds, at increased risk for placental insufficiency and growth retardation. Because hypertension, whatever the cause, may give rise to an increased incidence of growth retardation, both the resting blood pressure levels in the two positions and the positional blood pressure differences were investigated to detect possible relationships between these blood pressure parameters and growth retardation. Cross-sectional studies of pregnant nulliparous women in late pregnancy were performed to investigate these possibilities. The subjects were standardized as to age, gestational age and singleton pregnancy.

To remove observer or operator bias, terminal digit preference, prejudice and the influence of manipulation and conversation upon the blood pressure levels, an automated ultrasound device (Arteriosonde$^{R}$ 1217) was used in the study. Since we could find no previous studies providing information about the course of postural blood pressure differences during the whole of pregnancy, serial measurements of blood pressure and postural blood pressure difference were obtained in a smaller group of primigravid and multigravid subjects, including both normotensive and hypertensive individuals. These data were analyzed with regard to stability of the blood pressure differences and in relation to pregnancy outcome.

# PART I

# LITERATURE SURVEY

## 1.1 History

The first direct blood pressure measurement was accomplished by Stephan Hales in 1733 (quoted by WYKLICKY, 1966). A long tube was inserted into the crural artery of a horse: the column rose to a height of 2.40 m. Jean Poiseuille (quoted by WYKLICKY, 1966) repeated in 1828 these animal experiments using an U-shaped mercury manometer tube.

Around 1850 the first direct blood pressure measurement in a human subject was performed in France by J. Faivre by inserting a tube into an artery just after amputation of an arm (quoted by WYKLICKY, 1966). S. Ritter von Basch in 1880 (quoted by TROUT et al., 1956; COLLINS and MAGORA, 1963; WYKLICKY, 1966) is considered to have been the first to construct a sphygmomanometer for indirect blood pressure measurement, although J. Hérisson claimed to have described this device already in 1834. For practical purposes, the mercury was replaced by a metal plate in 1883. The principle of both systems consisted of measuring the pressure needed to occlude completely the radial artery, as demonstrated by disappearance of the pulse wave distally.

RIVA-ROCCI described in 1896 a mercury sphygmomanometer with an occluding cuff which is still used, although in a slightly different manner. The systolic blood pressure only was determined by palpation of the radial artery.

KOROTKOW used a stethoscope and introduced in 1905 the auscultatory method of blood pressure measurement. The indirect method of blood pressure measurement presently in common use should be called the Riva-Rocci-Korotkow method (WYKLICKY, 1966). The different sounds which can be heard on auscultation bear the name of Korotkow (BRAMWELL, 1940; KOSITSKII, 1958; CHUNGCHAROEN, 1964; LONDON and LONDON, 1967).

Another indirect determination of systolic and diastolic blood pressure has been developed which also uses an inflatable cuff, but employs Doppler-shift phenomena instead of audible sounds to

detect blood flow (see section 1.2.2.4).

## *1.2 Methods of blood pressure measurement*

### *1.2.1 Direct method*

Although the techniques presently used for the direct measurement of blood pressure are considerably less traumatic, and the apparatus vastly more sophisticated, than those used in the early, crude measurements, the principles remain the same. In present practice, the brachial or other artery is punctured, a small, flexible plastic catheter inserted and advanced 5 to 10 cm inside the artery. Several types of pressure transducers and strain gauges may be used (SIMPSON et al., 1968; HUNYOR et al., 1978).

The position of the strain gauge or pressure tranducer must be considered in relation to the subject's heart. If the catheter is inserted only over a limited distance into an artery, the strain gauge or transducer must be positioned at a midchest zero reference point. If the tip of the catheter lies in the heart and the gauge is attached to this tip, the position of the subject is not important. The response characteristics for strain gauges and pressure transducers are not the same and should be noted (SIMPSON et al., 1965; STEGALL et al., 1968).

Although the intra-arterial blood pressure determination is the most accurate method, it is too invasive for general use in large scale clinical practice and, in addition, carries the occasional hazard of permanent loss of the artery (STEGALL et al., 1968).

### *1.2.2 Indirect methods*

#### *1.2.2.1 Palpatory method*

This method uses external pressure to occlude the brachial artery. The arterial pulsations distal to the pressure site disappear when, for example, an inflated upper arm cuff connected to a manometer compresses the brachial artery completely. The air is

released slowly, manually or automatically, until the point is reached where the pulse is again detected by palpation (RIVA-ROCCI, 1896). This point is considered to be the systolic pressure.

*1.2.2.2 Auscultatory method*

If a stethoscope is placed distal to an occluding cuff, e.g. just over the brachial artery, and the cuff pressure is decreased gradually, various sounds can be heard (KOROTKOW, 1905). These sounds of Korotkow are indicative of blood flow under the constricting upper arm cuff. They are not derived from the heart sounds, but are generated by turbulent blood flow near the compressed segment of the artery (CHUNGCHAROEN, 1964).

Five phases of the sounds can be distinguished (BRAMWELL, 1940; KOSITSKII, 1958; COLLINS and MAGORA, 1963; CHUNGCHAROEN, 1964):

*Phase I.* A tone develops as the first jet of blood penetrates beyond the point of compression, and is audible as a sharp, light tap.

*Phase II.* The noise or murmuring sounds which follow after the initial sounds are due to the further, but still incomplete opening of the lumen of the artery.

*Phase III.* The murmuring sounds become loud, long and clear. BRAMWELL (1940) attributes this to a "breaker effect". The phenomena in the vessels are compared with waves breaking on the sea shore; the wave front becomes unstable and breakers are formed. The breaking pulse wave produces new waves which are shot out in front of it and cause turbulence in the blood.

*Phase IV.* At the end of phase III the sound becomes muffled and dull, indicating that, as the artery becomes less compressed, there is no longer a breaking-up of the advancing pulse waves.

*Phase V.* Complete disappearance of the sounds, indicating that the artery is no longer sufficiently compressed at any point in the pulse wave cycle, to produce turbulent flow. Thus, at all times the pressure in the artery exceeds that in the cuff.

The first appearance of the phase I tone is taken to represent the systolic blood pressure. The precise point in the succession of Korotkow sounds which indicates diastolic blood pressure is still disputed. Phase IV is considered by most authors as the diastolic pressure (KOSITSKII, 1958; COLLINS and MAGORA, 1963; FREIS and SAPPINGTON, 1968; GINSBURG and DUNCAN, 1969; VAN DONGEN, 1977). In some patients with aortic stenosis, however, phase IV Korotkow sounds do not occur because the pulse pressure wave rises so slowly that no breakers are formed. Therefore, BRAMWELL (1940) concluded that the true diastolic pressure must lie below the IVth Korotkow sound. The American Heart Association (BORDLEY et al., 1951) earlier considered phase V as the better one for determination of the end-diastolic pressure; but later, these recommendations were changed to the recording of both phases IV and V (KIRKENDALL et al., 1967). The Veterans Administration Co-operative Study Group (1970), PEART et al. (1977) and HUNYOR et al. (1978) used the disappearance of the Korotkow sounds (phase V), for the practical reason that phase IV could not be detected in most subjects.

Since the correlation of the Korotkow sounds with the simultaneous perception of the level of the mercury column is a rather subjective process, there are many possibilities for observer error or prejudice (see section 1.3.1.B).
To minimize these sources of error, ROSE et al. (1964) developed the London School of Hygiene sphygmomanometer. Three mercury manometers are mounted inside a cabinet. Each is connected to a plunger valve. The deflation rate is standardized to 2 mm/sec. The stethoscope is placed over the brachial artery. When the first sound of Korotkow is heard, the first plunger is depressed, resulting in occluding the mercury column in the first manometer. The same maneuver is performed when the IVth and Vth Korotkow sounds are heard. After complete deflation of the cuff, the door

of the cabinet is opened and only then can the results be read.

*1.2.2.3 Oscillometric method*

The visual oscillometric method is widely used by anaesthesiologists. An occluding arm cuff connected to a mercury or aneroid manometer is deflated until the oscillations of the mercury column or needle in the aneroid system show their greatest excursions. The lowest point of these excursions is taken as the systolic blood pressure. Diastolic blood pressure is shown by a sudden decrease in the oscillations. The systolic readings are fairly reliable, but the diastolic readings show a wide variation (COLLINS and MAGORA, 1963).

*1.2.2.4 Ultrasound blood pressure measurement*

A new method of blood pressure determination based on the principle of detecting arterial wall motions by the Doppler-shift signal was first suggested by WARE (1965). The transducer, containing two flat, thin chips of lead zirconate titanate, is positioned directly over the brachial artery (STEGALL et al., 1968; KIRBY et al., 1969). A standard upper arm cuff is inflated. One crystal produces ultrasound waves which penetrate all structures of the arm, while the other serves as a receiver. When the arterial wall begins to move, as obviously happens when the cuff deflates the shifted frequencies of the reflected ultrasound are received by the second piezoelectric element, amplified and filtered for display or made audible. When the artery is completely compressed proximal to the transducer, there are obviously no motions of the arterial wall. Although there are some movements of the wall of the completely patent artery, these are small and the Doppler shifts they produce fall below the detection threshold of the device. Thus the appearance and disappearance of relatively large excursions of the artery wall are taken to indicate, respectively, systolic and diastolic blood pressures.

The difference between Korotkow sounds and Doppler

shift signals is that the Korotkow sounds are produced by turbulence of blood flow (see section 1.2.2) and Doppler-shift signals by movement of the arterial wall.
The importance of this type of blood pressure measurement is that the procedure can be performed automatically, hard-copy records may be obtained, and observer bias is largely overcome, no auditory dependence exists and the method can be used accurately in subjects where the diastolic blood pressure is very low, as for example, in shock patients (KIRBY et al., 1969) and in children (ZAHED et al., 1971).

### *1.3 Variability in blood pressure readings*

All measurements, including blood pressure determinations, are subject to two kinds of errors: instrument and observer/operator errors (ROSE et al., 1964; KIRKENDALL et al., 1967). These sorts of errors are described here. In addition, a biological phenomenon such as blood pressure may exhibit true variations, which may, in turn, be due to either random or systematic factors affecting the individual. These variations will be described in chapter 2.

#### *1.3.1 Measurement errors*

##### *A Instrument*

A number of sources of error in the techniques of indirect blood pressure determination has been reviewed extensively by ROSE et al. (1964) and by the American Heart Association (KIRKENDALL et al., 1967).

##### *$A_1$ Air bag and cuff*

An air bag and cuff of the wrong size or shape may give rise to systematic errors in blood pressure measurements.
The inflatable air bag is surrounded by an unyielding cuff. If the bag is too narrow or too wide in relation to the size of the

arm, the blood pressure readings tend to be higher or lower, respectively, than the actual pressures. The standard adult cuff is 12 x 23 cm; however, the recommendation of the American Heart Association is that the bag should be 20% wider than the diameter of the arm (or leg). Both the arm circumference and the composition of the tissues may contribute to the higher indirect blood pressures found in obese patients because of loss of pressure across compressable substances (TROUT et al., 1956). The suggestion by TROUT et al. (1956) is to apply the arm cuff in obese patients around the forearm rather than the upper arm. KARVONEN et al. (1964) and SIMPSON et al. (1965) used a large bag, measuring 14 x 40 cm, and concluded that the measurement error due to the thickness of the upper arm is eliminated. However, the best correlation between the indirect and intra-arterial blood pressure measurements was found with a bag measuring 12 x 35 cm (SIMPSON et al., 1965).

FREIS and SAPPINGTON (1968) concluded, on the basis of comparisons of direct with auscultatory blood pressures, obtained with the standard 12 x 23 cm cuff, that the cuff pressure was incompletely transmitted to the compressed artery. As a result, the muffling of the sounds (phase IV) was heard at a higher cuff pressure than the actual diastolic blood pressure.

In yet another experiment comparing different cuffs, the direct and indirect blood pressures were measured in 31 patients. The results suggested that a wide cuff gives a more accurate pressure transmission as compared with a smaller cuff (ALEXANDER et al., 1977).

*A2 The manometer*

An improperly calibrated or malfunctioning manometer obviously may give an improper reading. The mercury manometer should be calibrated. The column of the manometer must be placed in the prescribed position, and the absence of dirt in the tube confirmed, in order to guarantee a correct blood pressure reading. The aneroid manometer should also be calibrated. The inflating system, exhaust valve and tubing should be checked frequently to

exclude leaks which could give rise to erroneous measurements (KIRKENDALL et al., 1967).

*A3 The stethoscope*

The design and acoustic characteristics of the stethoscope influence the transmission of the blood pressure sounds to the observer. Thus, these factors may influence blood pressure measurements. The longer the stethoscope tubing, the greater is the attenuation of the sound transmission. If the sounds are already of soft quality, the difference between Korotkow IV and V is not easily perceived (instrument and observer error). The stethoscope should be applied over the brachial artery and should not be in contact with the cuff, in order to avoid falsely elevated blood pressure readings (COLLINS and MAGORA, 1963).

*B Observer errors*

There are multiple sources of systematic observer errors or bias in the measurement of blood pressure by sphygmomanometry.

*B1 Systematic errors*

First, there is the custom of some physicians and nurses to record the diastolic blood pressure at the phase IV Korotkow sounds, while others take phase V to represent diastolic blood pressure, and very few individuals indicate which cut-off point they have employed. For example, HODES et al. (1975) sent a questionnaire on the detection and treatment of hypertension to a random sample of general practitioners. Phase IV was used as the end-diastolic pressure by 31%, phase V by 42% and both phases by 25%.

The results of the blood pressure measurement are further influenced by a long list of observer-related factors. These include such items as mental concentration, reaction time, hearing acuity, interpretation of sounds, visual acuity, the ability to read a moving column, the custom of watching the

meniscus of the mercury column from a particular angle, the rate of inflation and deflation of the cuff and the technique of applying the rubber bag and stethoscope more or less correctly (ROSE et al., 1964; EILERTSEN and HUMERFELT, 1968).
If these factors are more or less constant for a given observer, the sum of these systematic errors leads to consistent over- and underestimation of blood pressure. But these same variables will also cause inter- and intra-observer differences.
Wilcox (quoted by ROSE et al., 1964) used a sound film depicting the measurement of blood pressures of 7 subjects to test 349 graduate nurses. The estimates by the various observers for individual pressures had standard deviations which ranged from 4 to 16 mmHg for systolic blood pressure and 2 - 45 mmHg for diastolic blood pressure.
On the other hand, in the Bergen blood pressure survey 70.000 subjects were seen by 19 specially trained nurses (EILERTSEN and HUMERFELT, 1968). The subjects were examined in a standardized resting position. The variations of blood pressure readings by each observer did not indicate a real reading difference between the observers.
The factor of special training may account for the discrepancy in these two cited studies. However, the Wilcox study (quoted by ROSE et al., 1964) suggests that routine blood pressures recorded by clinical personnel must be accepted with some reservations.

If the cuff is not at the same height as the heart, the hydrostatic pressure difference must be added or subtracted depending on the position of the arm relative to the heart, because each cm of vertical height above or below the heart equals a difference in pressure of 0.7 mmHg (STEIN, 1952; SCHREIBER, 1954; BURTON, 1965; KIRKENDALL et al., 1967; ESKES et al., 1974; VAN DONGEN and ESKES, 1979). A standard positioning of the arm is therefore recommended by the American Heart Association. The position of the subject should be carefully noted (KIRKENDALL et al., 1967; ESKES, 1975), especially if the standard positioning is not employed.

*B2 Terminal digit preference*

The observer must mentally synchronize the visual image of a continuously moving column or needle with the intermittent acoustic signal of the Korotkow sounds. Depending on the rate of cuff deflation and heart rate, the indicated pressure may fall several mmHg between successive pulse beats. In addition, the observer cannot predict accurately just at what level the sounds may appear or change. Thus, he or she must estimate and interpolate the levels chosen as systolic and diastolic blood pressure. These uncertainties often lead to recording blood pressures in 2, 5 or 10 mmHg steps, and conscious and unconscious bias may result particularly in zero end-digit preference (ROSE et al., 1964; EILERTSEN and HUMERFELT, 1968; FRIEDMAN and NEFF, 1976). In 10% of the subjects in the Bergen blood pressure survey, the London School of Hygiene manometer (see Section 1.2.2.2) was used (EILERTSEN and HUMERFELT, 1968). The zero end-digit preference with the conventional sphygmomanometer amounted to 25%, as compared with only 14% when the London School of Hygiene manometer was used.

*B3 Prejudice*

If a decision to record a certain blood pressure level means that a subject becomes a patient or requires additional evaluation, the observer often tends to avoid recording blood pressures at this dividing point. This phenomenon is difficult to document; however, experience suggests strongly that it exists. OLDHAM (1960) and ROSE et al. (1964) have also presented evidence for the presence of this type of observer bias.

*1.4 Comparison between different methods*

*1.4.1 Intra-arterial versus Riva-Rocci method*

HENSCHEL et al. (1954) measured both the intra-arterial blood pressure and simultaneously the auscultatory blood pressure with

an aneroid sphygmomanometer in 11 healthy young men. The systolic intra-arterial blood pressure was always higher (5%-10%), and the diastolic blood pressure lower (15%-75%), than the blood pressures measured with the indirect method, both at rest and during work.

Systolic and diastolic pressures measured intra-arterially were also found to be higher and lower, respectively, than indirectly recorded levels by VAN BERGEN et al. (1954) in 70 non-pregnant subjects. Only graphs were given.

HUNYOR et al. (1978) compared the performance of seven types of sphygmomanometers (three manual and four more-or-less automated devices) with the blood pressure readings obtained simultaneously from intra-arterial catheterization in nine subjects. The systolic blood pressure was generally underestimated (range 7-31 mmHg) and the diastolic blood pressure overestimated (range 2-10 mmHg) with the sphygmomanometers as compared to the intra-arterial blood pressures. Pressure changes, however, were quite reliably measured.

In 70 pregnant normotensive, chronic hypertensive and toxaemic subjects the intra-arterial values were lower for both systolic (6 mmHg) and diastolic (15 mmHg) pressures than those recorded by use of a mercury sphygmomanometer (GINSBURG and DUNCAN, 1969). The recordings were performed under standardized conditions: the patients were allowed to rest comfortably in the supine position for at least half an hour before the measurements were made.

### *1.4.2 Intra-arterial versus ultrasound method*

The ultrasound blood pressure measurements correlate well with intra-arterial values. KEMMERER et al. (1967) compared blood pressures determined directly and by ultrasound: systolic and diastolic differences were only 0.5 and 1.2 mmHg, respectively.

Ten normotensive and one hypertensive subjects were examined by STEGALL et al. (1968) and here also a close agreement ($r=0.96$) was found between the direct arterial and ultrasound determinations.

Comparison between 195 direct blood pressure readings and 1903

indirect automated ultrasound blood pressure determinations (Arteriosonde , see section 7.1.3) proved to be very satisfactory, as was shown by HOCHBERG and SALOMON (1971). The mean systolic and diastolic differences between the automated ultrasound and intra-arterial measurements in this study were 0.5 (SD 7.3; r=0.96) and 7.6 (SD 5.7; r=0.92) mmHg, respectively.

### *1.4.3 Ultrasound versus Riva-Rocci method*

In a comparison of the ultrasound and auscultatory methods TE SELLE and THIEN (1977) found that the ultrasound systolic blood pressure was 3% lower than that determined from the first Korotkow sound. The diastolic blood pressure was 5% lower than the level of Korotkow IV and 1% higher than Korotkow V. Thus, the fifth Korotkow sound correlates well with the end-diastolic pressure as recorded by the Arteriosonde 1216, an automated ultrasound device.
Although DRAYER (1975) stated that the Doppler diastolic blood pressure corresponded with the fourth Korotkow sound, he presented no data to support this conclusion.

## *1.5 Conclusions*

The intra-arterial method obviously records the actual blood pressure. Thus, the actual systolic blood pressure is higher, and the real diastolic blood pressure lower, than those estimated with the mercury and aneroid sphygmomanometers.

However, very rarely is a clear statement made as to the relative positions of the patient, strain gauge or measuring cuff. This is important because of the hydrostatic pressure differences which are included in the blood pressure if the heart is not at the same level as the site of measurement.

A very good correlation between intra-arterial and ultrasound methods of blood pressure measurement has been established. The indirect ultrasound method may therefore be considered to be a reliable blood pressure recording system. However, it should be born in mind that, generally, ultrasound blood pressures

are lower than those determined with the auscultatory methods.

Since it is not yet clearly established which of the auscultatory measures of diastolic blood pressure (fourth or fifth Korotkow sounds) is closest to the real diastolic blood pressure, the level of both those sounds should be recorded.

Although the actual systolic and diastolic blood pressures may differ somewhat from those determined by either of the major indirect methods, the indirect methods appear to record changes in blood pressure in the same individual accurately.

Although the ultrasound method of measuring the blood pressure avoids most of the observer errors, there is still a discrepancy between the ultrasound blood pressure measurement and the true blood pressure measured intra-arterially. The ultrasound technique tends, on the average, to estimate systolic blood pressure quite accurately, but to overestimate diastolic blood pressure.

It is not the purpose of this thesis to go into details of the regulation of blood pressure and the extensive literature on this topic. This regulation was recently reviewed by GUYTON and JONES (1974), and the reader is referred to this textbook.
A summary of some of the important factors which contribute to the variability and variation of blood pressure would, however, seem to be in order at this point before proceeding further with the discussion of the effect of pregnancy upon the blood pressure.

## *2.1 Summary of blood pressure physiology*

The blood flow to all organs and tissues is maintained by the difference in pressure between the arterial and venous sides of the vascular system ("perfusion pressure"). This pressure differential is, in turn, maintained by the pumping action of the heart, together with the resistance to flow provided mainly by the small pre-capillary arterioles. This relationship is described very simply by the equation MAP = CO x R, where MAP represents mean arterial blood pressure, CO is cardiac output, and R indicates total peripheral vascular resistance. Blood viscosity, vessel elasticity, and the special features of pulsatile (as opposed to continuous) flow also affect blood pressure, but these effects are of small magnitude compared to the major determinants, CO and R.

Cardiac output is the product of heart rate and stroke volume. Many factors control the cardiac output. The heart rate is normally controlled by the pulsatile discharge of impulses by the sino-atrial node, which is influenced by the autonomic nervous system. Sympathetic stimulation causes acceleration of the heart

and parasympathetic or vagal stimulation causes slowing of the heart. Humoral influences, such as catecholamines, may influence the heart rate by direct action on the heart or also via the autonomic nervous system.

Stroke volume represents the difference between the end-diastolic and end-systolic ventricular volumes. Diastolic volume is dependent on filling pressure and the rate of blood flow into the ventricles, i.e. the venous return. This in turn, depends on the effective circulating blood volume and venous capacity. Diastolic volume is also affected by ventricular distensibility. The systolic volume is determined by the force of the myocardial contraction and the pressure in the outflow vessels. All these factors may be influenced by various neurohumoral stimuli. In addition, stroke volume and heart rate are highly interrelated, since in the interval between successive systoles is also the time available for ventricular filling.

The main source of resistance to flow through the vascular system is the small arteriole. Since resistance is inversely proportional to the 4th power of the vessel radius, small changes in the calibre of these vessels can result in major changes in resistance and, thus, in pressure and flow. The tone of the vascular smooth muscle in these arterioles is regulated both by systemic factors, including, importantly, circulating catecholamines and small polypeptides (angiotensin II, vasopressin, oxytocin and bradykinin) and by locally produced substances such as prostaglandins, kinins, and products of tissue metabolism.

Autonomic nervous system activity may affect the arterioles generally or only locally, depending on the nature and magnitude of the stimulus. Because of this selective and graded response pattern, autonomic activity is important in transient adjustments of vascular resistance to, for example, changes in posture.

According to present concepts, there are different types of receptors for autonomic neurotransmitters in the vascular smooth muscle (and in many other tissues as well), a situation which

explains both differing effects of the individual transmitters, and also the sometimes different effects of the same transmitter in different vascular beds.
In the vascular system, activation of the α-adrenergic receptors produces vasoconstriction, whereas stimulation of β-adrenergic receptors produces vasodilatation. Noradrenaline binds to and activates mainly the α-receptors, whereas small amounts of adrenaline activate predominantly α-adrenergic effects and large amounts of adrenaline mainly β-adrenergic effects.
Cholinergic receptors are almost as extensive as adrenergic receptors in the vascular beds, and their activation produces vasodilatation.

Reference to the equation given above, shows immediately that the arterial pressure can be increased or decreased by changes in the cardiac output or peripheral resistance. As a practical approximation, it can be considered that diastolic blood pressure is most highly influenced by peripheral resistance, whereas pulse pressure reflects largely cardiac stroke volume.

Short term regulation of blood pressure is effected by the baroreceptor reflex in combination with sympathetic and parasympathetic activity.
If, for example, a pregnant subject in late pregnancy turns from the lateral to the supine position, then a decreased venous return will occur due to compression of the inferior vena cava by the gravid uterus. The decreased blood volume in the atrium is reflected by a lessened tension of the atrial wall and an atrial mechanoreceptor will cause a decrease in heart rate by vagal stimulation (Bainbridge reflex).
The carotid sinus and aortic arch baroreceptors are mechanoreceptors which are localized in the adventitia of the arterial wall. The stretching will be followed by a decrease in heart rate. Thus the cardiac output decreases and regulates the level of the blood pressure (see equation). A negative feedback is also operating : when the arterial blood pressure rises or falls, then the parasympathetic or sympathetic

efferent pathways influence not only the heart rate, but also the cardiac contractility and (perhaps) the vascular capacity.

The medium term changes which control the level of the blood pressure are mainly brought about by the renin-angiotensin-aldosterone (RAA) system. Renin is a proteolytic enzyme, produced in the renal juxtaglomerular apparatus, which will split off from angiotensinogen (an α2-globulin, produced in the liver) a decapeptide, angiotensin I (A I). A converting enzyme reduces this AI to an octapeptide, angiotensin II (A II). A II directly induces vasoconstriction by an effect on the arterial wall. Via stimulation of aldosterone production, which gives rise to an increase in sodium reabsorption of the renal tubules, a vasoconstriction will occur under the influence of sodium by direct action on the arterial wall.
If changes in posture occur, or other factors which influence the renal blood flow, such as compression of the renal arteries or hypertension, renin production will change to maintain the homoiostasis of the renal functions. The chain of events described above will start and thus the blood pressure will be lowered or increased.

Anatomical changes in the precapillary arterioles can be permanent, as can be seen in patients with malignant hypertension. Thus renal blood flow is impaired and the blood pressure will be continuously high. The high blood pressure will try to maintain the renal blood flow and the glomerular filtration rate, triggered by the enhanced production of renin in the kidney.

### *2.2 Variation in blood pressure*

The blood pressure can vary also by changes in autonomic nervous and neurohumoral control.
An elevation of blood pressure can be caused by enhanced cardiac output with or without increased peripheral resistance or by an increased peripheral resistance without increased cardiac output.

*Random variation* can be defined as the difference in blood pressure between individuals and in an individual.

The *basal blood pressure reading* is "the level obtained when physical, metabolic, mental and emotional stimuli which elevate blood pressure have been eliminated" (definition used by the American Heart Association, KIRKENDALL et al., 1967). Usually this implies a lower level of both systolic and diastolic blood pressures, when compared with the blood pressure level obtained from casual readings.
Recent physical activity, temperature of the room, conditions of the climate, emotions and stress may influence the level of blood pressure readings, which are referred to as casual blood pressure readings. The casual blood pressure is therefore the level obtained without any consideration of environmental factors. Usually the systolic blood pressure is more elevated by external stimuli than the diastolic blood pressure (VARADY and MAXWELL, 1972).

If readings of different subjects have to be compared, investigations under standardized conditions are preferred, including the posture of the subject (MIALL and OLDHAM, 1958).

*The systematic variation* is a recurrent and consistent biological phenomenon, such as circadian rhythm, race, sex and age.

The highest levels of blood pressure in an individual during the day and night are usually to be found during the afternoon and early evening . The lowest pressures are recorded in the period from midnight to 4.00 hours. This nocturnal decrease is dependent upon both sleep and the rate of descent of sleep. If sleep is prevented the decrease at night was less than with sleep (PICKERING et al., 1967). The baroreceptor reflex sensitivity was increased during sleep in 9 of the 10 normotensive non-pregnant subjects studied, leading to a lower arterial pressure during sleep (PICKERING et al., 1968).

There is no clear relation between race and differing blood pressure levels. Other socio-economic factors appear to be responsible for the differences found.

The blood pressures in rural Nigerian women and men are lower compared to their descendants in North America (AKINKUGBE and OJO, 1968), indicating that other feeding habits, the stress of every day living and other unmeasurable influences could explain the difference.

The influence of age on both the systolic and diastolic blood pressure is clearly demonstrated in both the Framingham study (KANNEL, 1974) and the South Wales survey (MIALL and OLDHAM, 1963). The blood pressures of women are lower than those of men till the age of 45 years, after which age they exceed the male blood pressures.

A variation of blood pressure may fall in both categories of variations. For example, an elevation of blood pressure during emotional stress may be a repeatable systematic occurrence in the context of a casual blood pressure reading during physical examination. The period of emotional stress would fall in the random influence on blood pressure.

### *2.3 Conclusions*

The systemic arterial blood pressure is maintained by both the cardiac output and systemic vascular resistance.

The regulation of blood pressure is exerted by

- short time changes by the baroreceptor reflexes through the pathway of the autonomic nervous system and neurohumoral vasoactive substances;
- medium term changes by the RAA-system and
- long term changes by pathologic changes in the arterioles.

The variation in blood pressure is due to *random* variation, such as rest, posture, emotion and exercise, and by *systematic* variation, such as sleep, race, sex and age.

When blood pressures of individuals are compared, one should try to minimize the instrument and observer errors (Chapter I), and the random variations (basal readings). Because of the impossibility of influencing the systematic variations, only matched groups for age, race and sex should be compared.

In normal pregnancy several haemodynamic changes occur: the size of the uterine arteries increases greatly and the capacity of the venous draining system in the lower part of the body is augmented enormously. This enhanced vascular capacity is used by an increased blood volume.
A high blood flow, propelled by the heart with an increased cardiac output, in combination with the decreased systemic and uterine vascular resistance, facilitates the utero-placental circulation (ASSALI and VAUGHN, 1977).

## *3.1 Cardiac output*

The relation between cardiac output and blood pressure is described in section 2.1. Cardiac output in normal pregnant women increases progressively throughout pregnancy and its maximum of 30% to 50% above non-pregnant values is reached after 32 weeks of gestation (UELAND et al., 1969), but it decreases until term according to BURWELL (1938), ADAMS (1954) and WALTERS et al., (1966). However, in these three cross-sectional studies different techniques were used for patients in the *supine* position. BURWELL (1938) used an acetylene technique in 4 patients, ADAMS (1954) and WALTERS et al. (1966) used a dye dilution technique in 31 and 30 subjects, respectively.
The influence of the supine position upon the cardiac output will be discussed in section 4.1.

All patients in late pregnancy showed a striking increase in cardiac output when compared with the non-pregnant subjects, if the estimation of the cardiac output was made in a lateral position.
PYÖRÄLÄ (1966) found in 12 patients, who were cross-sectionally studied with a dye dilution method, a steadily maintained rise of 1.7 l/min above the levels in control subjects. No decline

was found till term.
LEES et al. (1967) could not demonstrate a fall in cardiac output in late pregnancy in their 5 subjects in left lateral position. The serial measurements were made with a dye dilution method. UELAND et al. (1969) measured serially the cardiac output, heart rate and stroke volume in 11 normotensive subjects. The cardiac output was determined after injection of indocyanine green. The maximal cardiac output was found at the 32nd week of pregnancy and it decreased until term.

The augmented cardiac output in pregnancy is caused by an increase in both heart rate and stroke volume. The heart rate increases progressively in pregnancy by about 15 beats per minute (HYTTEN and LEITCH, 1971). The enlarged stroke volume is described by WALTERS et al. (1966), HYTTEN and LEITCH (1971) and ASSALI and VAUGHN (1977).

### *3.2 Peripheral resistance*

In section 2.1 it has been already discussed that the peripheral resistance is necessary to offer resistance to the blood flow in order to maintain a certain blood pressure level. The vascular resistance during pregnancy decreases. The vascular resistance from mid-pregnancy till term was calculated in the cross-sectional studies of BADER et al. (1955) and PYÖRÄLÄ (1966). They found, during the 20th week of gestation a resistance of 986 and 979 dynes sec.cm$^{-5}$, respectively, it rose progressively during the remaining time of pregnancy and reached values of between 1200 - 1300 dynes sec.cm$^{-5}$, whereas non-pregnant control subjects had a resistance of about 1700 dynes sec.cm$^{-5}$. The peripheral resistance is calculated by the equation mentioned in section 2.1, during the measurement of the cardiac output. DILTS et al. (1969) calculated the systemic vascular resistance in pregnant and non-pregnant sheep and found 0.9 and 1.5 mmHg/ml/min/kg, respectively. Uterine vascular resistance was about ten times lower in the pregnant sheep when compared with the non-pregnant sheep (5.7 and 55 mmHg/ml/min/kg). This low resistance vascular bed appears to be the factor which facilitates the

utero-placental blood flow in the pregnant subject. Both the increased cardiac output and blood volume, together with this decrease in vascular resistance, are able to fulfil the needs of the uterus and placenta. The vascular reactivity in normotensive, hypertensive and pre-eclamptic patients will be discussed in chapter 6.

### *3.3 Course of blood pressure during normal pregnancy*

Arterial blood pressures have been recorded throughout pregnancy in cross-sectional and longitudinal blood pressure surveys by various authors. The details of their studies are summarized in Table 3.3.

The so-called *mid-pregnancy dip* seems to be a common factor in normotensive subjects, except for the subjects studied by BREHM and KINDLING (1955), SCHWARZ (1964), MacGILLIVRAY et al. (1969), SHAPER et al. (1969) and VAN DONGEN (1977). The three last authors found no indication of mid-pregnancy dip in the second trimester of pregnancy in African and West Indian gravidae of African origin, respectively, while in Indian primigravidae a clear drop was noted (SHAPER et al., 1969).

The variability of casual blood pressure measurements was studied by ARMITAGE and ROSE in 1966. Ten subjects were studied in sitting position by one observer using hte London School of Hygiene sphygmomanometer (see section 1.2.2.2). The blood pressure was recorded straight away after entrance in the room and repeated after two minutes. During 6 weeks 40 readings in each subject were performed. The variations seen in the occasional blood pressure determinations showed for the systolic blood pressure a downward trend and for the diastolic blood pressure a fall of 8 mmHg from the first to the third blood pressure reading and then a downward trend to the end of 12 mmHg. It is suggested by these authors that the mid-pregnancy dip can be explained by this phenomenon.

No differences in blood pressure levels and course between nulliparae and multiparae were found by SCHWARZ (1964), although

TABLE 3.3 COURSE OF BLOOD PRESSURE DURING NORMAL PREGNANCY

| | | Methods * | | | | |
|---|---|---|---|---|---|---|
| Authors | Subjects | Study | Positions | Korotkow | Statistics | Remarks |
| BREHM and KINDLING (1955) | 27 mostly P | CP | Supine | - | - | No mid-pregnancy dip; nadir SBP 8th month, nadir DBP 6th-7th month. |
| SCHWARZ (1964) | 83 M + P | LP | Supine | V | Regression analysis | No mid-pregnancy dip; slight↓BP in early pregnancy, ↑towards non-pregnant levels at term. |
| MacGILLIVRAY (1969) | 226 P | LP | Supine | IV LSHS | Regression analysis | Mid-pregnancy dip; ↓BP 1st and 2nd trimester, in 3rd trimester,↑DBP>↑SBP. |
| | 9 P West Indian | LP | Supine | IV LSHS | Regression analysis | No mid-pregnancy dip; small, insignificant↑. |
| SHAPER et al. (1969) | 139 P African | CP | Sitting | IV | Regression analysis | No mid-pregnancy dip; slight↑during pregnancy. |
| | 127 P Indian | CP | Sitting | IV | Regression analysis | ↑after mid-pregnancy dip. |
| ESKES et al. (1974) | 17 M + P | LP | Sitting/ supine/left lateral | V | Two-way analysis of variance | Mid-pregnancy dip not specified, ↑DBP after 26th week irrespective of posture. |

| | | | | | | |
|---|---|---|---|---|---|---|
| CHRISTIANSON (1976) | 6662 M + P Whites | CR | - | - | One-way analysis of variance | Mid-pregnancy dip; ↓DBP>↓SBP; late pregnancy↑. |
| PAGE and CHRISTIANSON (1976 a) | 14.833** Whites and Blacks | CR | - | - | Regression analysis; analysis of variance | Mid-pregnancy dip; BP↑after mid-pregnancy dip. |
| CHESLEY (1976) | 1400 P** Whites | CR | - | - | Frequency distribution | Mid-pregnancy dip; ↑DBP>↑SBP between 32-36 weeks. |
| VAN DONGEN (1977) | 146 P*** African | CP | Sitting | IV | Regression analysis | No mid-pregnancy dip; no late pregnancy↑, throughout pregnancy, BP<non-pregnant controls. |
| GALLERY et al. (1977) | 67 M + P | LP | Sitting/ left lateral | V HRZS | - | Mid-pregnancy dip; ↓in early pregnancy ↓in last month |

P, primigravidae; M, multigravidae; CP, cross-sectional prospective; LP, longitudinal prospective; CR, cross-sectional retrospective; -, not specified; SBP, systolic blood pressure; DBP, diastolic blood pressure; LSHS, London School of Hygiene Sphygmomanometer; HRZS, Hawkesley random-zero sphygmomanometer

* Methods of measurement: Riva-Rocci Korotkow, unless specified otherwise.

** Matched for age (25-34 years)

*** Matched for age (15-19 years)

CHRISTIANSON (1976) observed that each age group of nulliparae had both higher systolic and diastolic blood pressures than primiparae. The highest blood pressures were found 6 weeks after delivery (MacGILLIVRAY, 1969). The decrease in diastolic blood pressure tends to be relatively more marked than in systolic blood pressure, leading to higher pulse pressures in the first two trimesters of pregnancy (MacGILLIVRAY et al., 1969).

In some studies the patients were matched for age: in the Collaborative Perinatal Project (CHESLEY, 1976 ) 1400 white nulliparous subjects were described in the age group of 25 - 34 years; the same applies to the patients of CHRISTIANSON (1976) and PAGE and CHRISTIANSON (1976a). The 146 African primigravid subjects described by VAN DONGEN (1977) were 15 - 19 years old and were chosen because the first pregnancies mainly occur at the age of 16.

In conclusion one might say that the course of blood pressure in pregnant European women is lowered in the first two trimesters and rises in the third trimester. The diastolic blood pressure in particular is considerably below non-pregnant levels leading to an enhanced pulse pressure in the first two trimesters. A mid-pregnancy drop seems to be a common feature in normal human pregnancy.

### *3.4 Factors causing systematic variation in blood pressure*

The reader is referred to section 2.2 where the definition of systematic variation has been given.

#### *3.4.1 Hypertension in pregnancy*

MacGILLIVRAY (1961) demonstrated in his survey of 4215 primigravidae that blood pressure levels rose progressively throughout pregnancy. Thus, no mid-pregnancy dip was found, and the level of blood pressures at the 20th week of gestation was similar to that in non-pregnant women in the same age group. It turned out that most patients were considered to be toxaemic

or pre-eclamptic in later pregnancy.

The increased vascular resistance in pre-eclampsia could be the explanation for the fact that this mid-pregnancy dip is absent in patients who developed pregnancy induced hypertension (MacGILLIVRAY, 1961, GALLERY et al., 1977). However, an exaggerated decrease in blood pressure was observed in hypertensive women during pregnancy by CHESLEY and ANNITO (1947), BROWNE (1947), MORRIS (1958) and TOWNSEND (1959).

The peripheral vasodilatation and the decreased vascular resistance cause a relative hypotension. The systolic and diastolic blood pressures in normotensive patients studied by GALLERY et al. (1977) significantly decreased. This decrease was already present in the 17th till the 20th week of pregnancy. However, the women who developed pregnancy induced hypertension did not show this mid-pregnancy dip.

### *3.4.2 Circadian rhythm*

BROOKS and CAROLL (1912) and PICKERING et al. (1967) recorded a greater fall in systolic blood pressure at night in hypertensive subjects as compared with normotensive subjects. However, when both systolic and diastolic blood pressures were measured, it was demonstrated by various authors that the relative decrease of blood pressure at night in hypertensive patients was less marked than in normotensive subjects (SHAW et al., 1963; RICHARDSON et al., 1964; DRAYER, 1975). No difference in circadian rhythm was noted by IRVING et al. (1974) and SCHMIDT et al. (1974).

Normotensive pregnant women in the last trimester of pregnancy show the same circadian rhythm in blood pressure as non-pregnant subjects (see section 2.2) according to SELIGMAN (1971), REDMAN et al. (1976 a ; 1976b), DAME et al. (1977) and MURNAGHAN et al. (1979), as is shown in Table 3.4.2.
Pregnant subjects with uncomplicated chronic hypertension do not show very much difference in the nocturnal decrease in the diastolic blood pressure, but sometimes they do show a little increase in systolic blood pressure when compared with

TABLE 3.4.2 INFLUENCE OF SLEEP UPON THE BLOOD PRESSURE OF NORMOTENSIVE, CHRONIC HYPERTENSIVE AND PRE-ECLAMPTIC PREGNANT WOMEN IN THE LAST TRIMESTER OF PREGNANCY

| Authors | Subjects | Methods | Change in BP at night* |
|---|---|---|---|
| SELIGMAN (1971) | 10 N<br>10 C<br>10 PE | Oscillographic, every 5 min/24 hrs, posture not specified | N : -50%<br>C : -55%<br>PE: -30% |
| REDMAN et al. (1976 a) | 9 N<br>9 C<br>17 PE | Ultrasound, every 10 min/24 hrs, posture not specified | N : SBP -12; DBP -4.8<br>C : SBP -16; DBP -6<br>PE: reversal (10 patients) SBP +14; DBP +10 |
| REDMAN et al. (1976 b) | 16 C<br>3 PE | Ultrasound<br>every 10 min/24 hrs left lateral position. | C : SBP -10 to +19; DBP -6 to -12<br>PE: reversal SBP +14; DBP 0 to +20 |
| DAME et al. (1977) | 6 N<br>6 PE | Arterial catheter, every 5 min/4 days, posture not specified | N : SBP and DBP 0 to -20<br>PE: reversal SBP and DBP 0 to +20 |
| MURNAGHAN et al. (1979) | 16 N<br>15 C<br>15 C<br>8 PE | Arterial catheter, continuous 3 days, unrestricted | N, C}: same as non-pregnant<br>PE: reversal (values not given) |

N, normotensive; C, chronic hypertension; PE, pre-eclampsia; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure.

* : mmHg unless otherwise specified.

normotensive subjects (REDMAN et al., 1976b; see Table 3.4.2). However, patients with severe pre-eclampsia consistently show a decreased fall of blood pressure during the night, with even a reversal of this pattern especially between 1.00 and 4.00 hours (REDMAN et al., 1976a; 1976b; DAME et al., 1977).
It should be noted that three different methods of blood pressure recording were used: ultrasound, intra-arterial and oscillographic (see Table 3.4.2). Postures were not standardized, except in those subjects studied by REDMAN et al. (1976b), who were placed in the left lateral position.

### *3.4.3 Socio-economic factors*

In a cross-sectional study of 127 Indian and 139 African primigravidae SHAPER et al. (1969) demonstrated higher levels of blood pressure in the Indian group as compared with the African group; after a mid-pregnancy dip both the systolic and diastolic blood pressures increased till term in the Indian primigravidae. In the African group no mid-pregnancy dip nor rising levels during pregnancy were noted. Biochemical parameters (cholesterol, triglycerides and phospholipides) had higher levels in the Indian primigravidae than in the African ones, suggesting a causative factor such as intake and availability of food.

The same socio-economic factors were thought to be responsible for the absence of both the mid-pregnancy drop and the rise in blood pressure in a cross-sectional study of 147 African primigravidae (VAN DONGEN, 1977).

MacGILLIVRAY et al. (1969) found that pregnant West Indian women had the lowest blood pressures and also only a very small rise of blood pressure during pregnancy in comparison with British and Irish subjects. CHRISTIANSON (1976) found no difference in the levels of the blood pressures in the 2nd trimester between pregnant white and black American subjects, which strongly suggests the influence of the environment.

## *3.5 Factors causing random variation in blood pressure*

The reader is referred to section 2.2 where the definition of random variation has been given. The same factors which disturb the basal blood pressure readings apply also to pregnant women (see section 2.2).

SCHWARZ (1964) studied 83 normotensive pregnant subjects throughout pregnancy under standardized conditions. The patients were put at rest in the recumbent supine position and the examinations performed in a familiar atmosphere. The conversation was confined to greetings only in order to exclude external stimuli as much as possible.

GINSBURG and DUNCAN (1969) compared direct and indirect blood pressure determinations between 17 normotensive, 13 chronic hypertensive, 23 "mild" toxaemic and 23 "severe" toxaemic patients (see section 1.4.1). Manipulation and conversation augmented the blood pressure levels. HOVINGA et al. (1978) arrived at the same conclusions in 7 toxaemic patients, in whom intra-arterially blood pressures were measured (see section 4.2.2).

## *3.6 Conclusions*

Cardiac output in pregnancy shows an increase of 30% to 50% as compared to non-pregnant levels due to both increased heart rate and stroke volume.

Systemic peripheral and uterine vascular resistance in pregnancy is greatly diminished.

The increase in the volume of circulating blood and flow rate (as compared to the non-pregnant state) is necessary in order to fulfil the needs of the augmented utero-placental circulation.

The decrease in diastolic blood pressure in early pregnancy tends to be relatively lower than the decrease in systolic blood pressure, giving rise to a higher pulse pressure than in the non-pregnant state and in the period late in pregnancy. The diastolic blood pressure tends to rise more than the systolic blood pressure till term. A lower pulse pressure develops after a mid-pregnancy dip.

The mid-pregnancy dip reflects a decreased peripheral resistance.

No mid-pregnancy dip occurs in the case of different eating habits (due to poverty). The blood pressures in pregnancy are lower than in non-pregnant state and thus a continuous low systemic peripheral resistance may exist throughout pregnancy.

In hypertensive pregnancy, with an increased resistance, no mid-pregnancy dip is seen.

Blood pressure falls at night, but less in hypertensive patients. A reversal at night is often seen in pre-eclamptic patients.

Manipulation and conversation during blood pressure measurements can alter the measurements. To compare results, the blood pressure should be determined under standardized conditions, in which methodology, posture and statistical analysis are specified.

The effects of the blood pressure upon the pregnancy and the pregnancy outcome are described in Chapter 5.

# CHAPTER 4 DIFFERENCES IN BLOOD PRESSURE BETWEEN SUPINE AND LEFT LATERAL POSITIONS

## 4.1 Supine hypotensive syndrome and aortocaval compression

The first author who described this clinical syndrome appears to be HANSEN (1942) (see Table 4.1).
McROBERTS (1951) described 6 case histories of postural shock out of 50 unselected patients. Usually the supine blood pressure was found to be lower than in the lateral positions, even when the supine hypotensive syndrome did not develop.
LEMTIS and SEGER (1973) reviewed the literature and found about 100 cases of the supine hypotensive syndrome. Ten new cases were added by the same authors in 1974. Various circumstances triggered off the occurrence of this syndrome: amnioscopy in the supine position, preparation for operation and even a forceful impression by a monaural stethoscope. All hypotensions developed after at least two minutes of continuous supine position.

The typical picture develops in a pregnant woman in her late pregnancy lying on her back with feelings of fainting accompanied by a marked fall in blood pressure. This vaso-vagal fainting syndrome (LEES et al., 1967) can be mistakenly understood as a real shock and eventually lead to a caesarean section (HOWARD et al., 1953).
The clarification of this phenomenon is understood by nearly all authors (Table 4.1); compression of the inferior vena cava with subsequent decreased venous return to the heart, resulting in reduced atrial filling, followed by a fall in cardiac output. After a few minutes a marked fall in blood pressure, vascular resistance and heart rate develops, resembling the vaso-vagal fainting syndrome and is called the "Supine Hypotensive Syndrome". This name was given by HOWARD et al. (1953) who rediscovered that the symptoms can be relieved easily by turning the patient on her

TABLE 4.1 SUPINE HYPOTENSIVE SYNDROME (SHS) AND AORTOCAVAL COMPRESSION

| Authors | Patients | Methods* | Findings (remarks apply to supine position unless specified) |
|---|---|---|---|
| HANSEN (1942) | 57 in late pregnancy | RR | SHS 7 (12%); impaired venous return. |
| HOWARD et al. (1953) | 160 in late pregnancy | RR | SHS 18 (11.2%); BP usually lower in supine position vs left lateral position |
| QUILLIGAN and TYLER (1959) | 196 in late pregnancy | RR and arterial catheter | SHS 1 (0.5%); C.O. not ↓; femoral venous pressure↑. |
| HOLMES (1960) | 500 M and P >36 weeks | RR | SHS 10 (2%); Postural hypotension less marked if foetal head engaged. |
| VORYS et al. (1961) | 31 M and P in late pregnancy | Arterial catheter | C.O.↓; femoral venous pressure↑. |
| WRIGHT (1962) | 100 M and P >36 weeks | RR | SHS 10 (10%) ; sitting vs supine vs lateral, BP lowest in supine pos. |
| SCOTT and KERR (1963) | 9 in late pregnancy | Cannulation of inferior vena cava | Obstruction at level L4-5; vascular resistance↑; compression as high as fundus. |
| KERR et al. (1964) | 12 (8 for s.c.; 4 anencephalic 38-40 weeks | Caval angio-grams | Occlusion of inf.vena cava is normal in pregnancy ; collateral venous system; left side more compressed than right side. |
| KERR (1965) | 6 in late pregnancy | Arterial catheter | C.O.↓; vascular resistance↑; foetal hypoxia. |
| LEES et al. (1967) | 8 in late pregnancy | Arterial catheter | SHS : 5 out of 8 patients with heads unengaged No supine-lateral BP difference |
| | 6 in late pregnancy | Arterial catheter | C.O.↓; vascular resistance ↑. |

Table 4.1 - continued -

| Authors | Patients | Methods | Findings |
|---|---|---|---|
| BIENIARZ et al. (1966) | 3 M + 2 P 34 weeks | Arterial catheter | Compression of aorta by uterus (see text) |
| BIENIARZ et al. (1968) | 70, 27 weeks<br>30 controls | Serial angiograms | Direct and indirect compression of aorta by uterus (see text) |
| SCANLON (1974) | 28 | Ultrasound | ↓Femoral artery pressure in hypertensive patients; aortic compression |
| ECKSTEIN and MARX (1974) | 72 first stage of labour | RR | ↓Femoral artery pressure; aortic compression |
| DRUMMOND et al. (1974) | 40 in late pregnancy<br>25 in early puerperium | RR | ↓Femoral artery pressure; leftward tilt reduces hypotension<br>No ↓femoral artery pressure |
| CAMPBELL (1978) | 20 normotensive subjects 30 weeks | London School of Hygiene Sphygmomanometer | Femoral artery SBP (no change in DBP) |

* : all prospective cases

RR, Riva-Rocci; P, primiparae; M, multiparae; C.O., cardiac output; SHS, supine hypotensive syndrome; BP, blood pressure

side.

SCOTT and KERR (1963) cannulated the inferior vena cava in 9 subjects in late pregnancy and found that the pressures were high from 18 - 35 mmHg. The venous pressure in the legs was also increased and this was even more enhanced if the uterus showed a contraction. If the catheter was pushed upward , the pressure fell markedly after passing the diaphragm; at withdrawal a total block over 5 cm long was seen 15 cm below the diaphragm. Below this obstruction lower pressures were recorded and these subjects did not suffer from the supine hypotensive syndrome; consequently it was concluded that venous collateral vessels were sufficient to drain the blood below the obstruction. During caesarean section it was observed that the inferior vena cava was completely occluded by the gravid uterus.

The complete occlusion of the inferior vena cava in supine position of subjects in late pregnancy is a normal feature, as was demonstrated by KERR et al. (1964) by means of serial caval angiograms in 12 patients. The venous return was diverted via the vertebral and azygos systems.

In the lateral position this obstruction is partly relieved, as was observed by means of X-rays (KERR et al., 1964). Apart from this, a fall in blood pressure which still remained at a level above the normal values, was noted (SCOTT and KERR, 1963).

In six patients the inferior vena cava just below the renal veins was manually occluded during 2.5 minutes after caesarean section and no change in blood pressure was detected (HOWARD et al., 1953).

In nine patients after caesarean section the same procedure was followed and no marked fall of systemic arterial blood pressure was found, whereas the venous pressure in the inferior vena cava rose to the pre-operative level (SCOTT and KERR, 1963).

Most women in late pregnancy can tolerate caval occlusion in the supine position and this means that the venous collateral circulation via the vertebral and azygos systems is adequate and in those women who show the supine hypotensive syndrome, inadequate (SCOTT and KERR, 1963; KERR et al., 1964; KERR, 1965).

The femoral venous pressure is increased and this is one reason for the increased occurrence of varicose veins in pregnancy

(HOLMES, 1957; QUILLIGAN and TYLER, 1959; VORYS et al., 1961; SCOTT and KERR, 1963)

In subjects with the supine hypotensive syndrome it was found by HOLMES (1960) and WRIGHT (1962) that a severe hypotension developed only when the foetal head was not yet engaged. The three patients of KERR (1965) with the foetal heads engaged showed an increase of cardiac output in the supine position of 8.2% as compared with 24.5% in the three subjects in whom the foetal heads were not engaged. KERR (1965) suggested other haemodynamic changes, but could not give an explanation for this association.
LEES et al. (1967) observed that the changes in right atrial pressure, cardiac output and peripheral resistance were smaller in those subjects in whom relative fixation of the uterus was provided by engagement of the foetal head, than in those in whom the presenting part was floating.
ECKSTEIN and MARX (1974) found in their 72 unselected subjects in the first stage of labour that the femoral hypotension was more strongly present in the 27 patients who were in active labour than in the 45 who were in the later phase of labour, which suggests less aortocaval compression in the latter group of patients.

In short, it seems that the descent of the foetal head can reduce the sequelae of the aortocaval compression.

Postural shock was observed in patients in late pregnancy when spinal anaesthesia was administered and the patient turned to the supine position to perform the planned caesarean section. HOLMES (1957) described 17 such patients. CAPPE and SURKS (1960) found only one case in 2000 subjects who were delivered by caesarean section under spinal anaesthesia. The shock was relieved by tilting the pelvis towards the left lateral position.
An instrument was even designed to maintain the left uterine displacement in order to fight this maternal hypotension during the operation (KENNEDY, 1970).

The maternal hypotension in 7 subjects with spinal anaesthesia caused depression of the newborns (GOODLIN, 1971a) and the lateral or semilateral positions are therefore strongly recommended both on the operation table and in the labour room (GOODLIN, 1971 a, b).

Summarizing, it seems that some patients in the last months of pregnancy are predisposed,due to a sudden decrease of the vasomotor tone, to develop the "Supine Hypotensive Syndrome" which leads to postural shock symptoms. These symptoms can be easily relieved by turning the patient to her side or by emptying the uterus. The train of events starts with the compression of the inferior vena cava in patients with an inadequate venous collateral system.

The phenomenon of compression of the inferior vena cava was investigated on a large scale, whereas the aortic compression was not considered at all till 1966 (see Table 4.1).

BIENIARZ et al. (1966) measured intra-arterially both femoral and brachial arterial blood pressures in five subjects in late pregnancy. Two were primigravidae and 3 multigravidae. The femoral blood pressure was found to be higher than the brachial blood pressure, but only in hypertensive patients. Both pressures were equal in normotensive subjects. In a patient who developed the supine hypotensive syndrome, the femoral systolic blood pressure was considerably lower than the brachial blood pressure. A low pulse pressure was the result. Also the maternal heart rate decreased. This phenomenon was later called the Poseiro-effect (POSEIRO et al., 1969). These findings suggested a compression of the aorta by the uterus.

An outstanding investigation in patients in late pregnancy was done in 1968 by BIENIARZ et al. In the case of 70 patients serial angiograms were made in late pregnancy as well as in 30 non-pregnant controls; with both groups the angiogram was made with the subject in supine position. The subrenal parts of the aorta were displaced to the left lateral, cranial and dorsal directions. If the uterus was dextroverted and dextrorotated,

the aorta was displaced to the left, as was the case in 67 out of the 70 pregnant subjects. During a contraction a small surface of support with high pressure was seen at the lumbar level L4-5, but when the uterus was relaxed between the contractions, the flow in the right renal artery was diminished and the left renal vein occluded, the latter giving rise to a retrograd flow into the left ovarian vein. It was concluded that direct aortocaval obstruction occurred at level L4-5; an indirect mechanical effect between the contractions was suggested on both the right side of arterial supply to the visceral organs and the left side of the venous drainage. Arterial hypotension enhanced the partial obstruction of the aorta and its branches in a relaxed uterus. In short, a gravid uterus in late pregnancy divides the circulation into two parts: at the caudal side not only the arterial pressure increases (and hence the impaired blood flow) but also the venous pressure; at the cranial side it is the reverse.

Due to the aortic compression in the supine position a relative hypotension in the lower limbs is observed by BIENIARZ et al. (1968), GOODLIN (1971a), ECKSTEIN and MARX (1974) and DRUMMOND et al. (1974). During a contraction the femoral pulse height decreases, indicating a hypotension. This phenomenon is called the Poseiro-effect (POSEIRÓ et al., 1969; Figure 4.1).

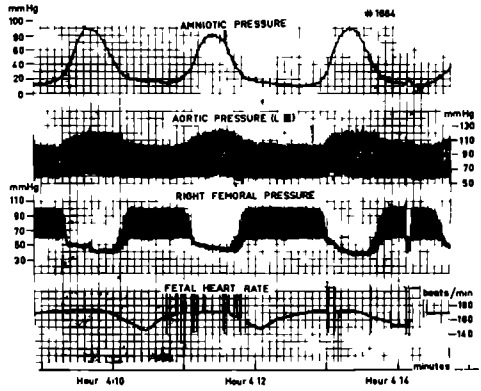



Fig. 4.1 Poseiro effect. By courtesy of J.J. Poseiro. Reference : Poseiro, J.J., Méndez-Bauer,C., Pose,S.V. and Caldeyro-Barcia (1969). Effect of uterine contractions on maternal blood flow through the placenta. Perinatal Factors Affecting Human Development, Pan American Health Organisation scientific publication, 185, 161.

The diastolic blood pressures, measured in the legs, in hypertensive patients were found to be considerably lower compared with those of normotensive pregnant and non-pregnant control subjects (SCANLON, 1974). The aortic narrowing in the supine position is shown by SCANLON (1974) in both a group of 12 hypertensive and a group of 8 normotensive pregnant subjects but not in 8 subjects in the puerperium. The diastolic blood pressures in the legs were lower in the hypertensive than in the normotensive subjects. Vasopressor responses to diminished uterine blood flow are mentioned in the aetiology of pregnancy induced hypertension ("uteroplacental ischaemia").
However, CAMPBELL (1978) did not find a decrease in the diastolic blood pressure of the legs but only a fall in systolic blood pressure in 20 normotensive pregnant subjects at a gestational age of 30 weeks , compared with values obtained six weeks post partum.

Thus, compression of the aorta can give rise to a diminished utero-placental blood flow and even cause foetal distress (BIENIARZ et al., 1966; BIENIARZ et al., 1968; REED et al., 1970; GOODLIN, 1971a; GOODLIN 1971b; HUMPHREY et al., 1973; LEMTIS and SEGER, 1974b), The obvious treatment is to turn the patient to the left side.

The cardiac output in the supine position is decreased due to the compression of the inferior vena cava as has already been mentioned in section 3.1.
VORYS et al. (1961) measured the cardiac output with a dye dilution technique in 31 normotensive pregnant women in late pregnancy. A significant decrease of 13% of the cardiac output was found in the supine position as compared with the left lateral position. The five non-pregnant control subjects showed no difference in cardiac output in the different positions and had lower cardiac outputs than the pregnant group (6.3 l/min and 8 l/min, respectively, in left lateral positions).
KERR (1965) realized and succeeded to prove that the compression of the gravid uterus on the inferior vena cava in the supine position was the cause of the decreased cardiac output. The

cardiac output was determined by a dye dilution technique in six normotensive patients in late pregnancy. When turned from the left lateral to the supine position the measured cardiac output fell from 4.0 to 3.0 l/min/sq.m.
Also a fall in cardiac output in the supine position was found by PYÖRÄLÄ (1966); LEES et al. (1967) and UELAND et al. (1969), compared to the cardiac output measured in left lateral position, which points to a compression phenomenon (see section 3.1). The heart rate does not rise but the systemic vascular resistance increases (KERR, 1965; LEES et al., 1967).

### *4.2 Left lateral versus supine position*

#### *4.2.1 Non-pregnant subjects*

The rotation of the body from the supine to the right or left lateral position causes a shift of the heart towards that side (ZDANSKY, 1949; STEIN, 1952; SCHREIBER, 1954; COOLEY and SCHEIBER SCHREIBER, 1968). This is radiologically confirmed; in the lateral positions the diaphragm rises on the ipsolateral side and descends on the contralateral side. The apex of the heart is elevated, the heart itself is shifted towards the side on which the patient lies and is clockwisely rotated. These changes are more visible in the left lateral than in the right lateral position (ZDANSKY, 1949; COOLEY and SCHREIBER, 1968).
The measured fall in both systolic and diastolic blood pressures in the left lateral when compared with the supine position, is recorded immediately after postural change, indicating a hydrostatic difference (SCHREIBER, 1954; BURTON, 1965). The recommendation of the American Heart Association (KIRKENDALL et al., 1967) include "a standard positioning of the forearm at the horizontal level of the fourth intercostal space at the sternum" in order to exclude the hydrostatic difference in the measured blood pressure. SCHREIBER (1954) noted a marked hypotension (for both systolic and diastolic blood pressures 10 mmHg difference) in 186 out of 206 male patients in the left lateral position when compared with the level of the blood

pressures in the supine position. Hydrostatic differences and baroreceptor reflexes are thought to be the responsible factors. Other workers, however, did not consider this phenomenon to be important. The majority of the 100 male patients of STEIN (1952) showed this postural blood pressure change and different explanations are given to elucidate this difference, except the hydrostatic factor.
The same applies to TROWER and WALTERS (1968) who found in their 14 non-pregnant control subjects a postural difference of 15.3 and 15.0 mmHg for systolic and diastolic blood pressures, respectively, when the subjects were turned from the left lateral to the supine position (auscultatory method).
The blood pressure was measured intra-arterially by LEES et al. (1967) and LUCAS et al. (1979) in non-pregnant patients in the supine and the left lateral positions. In the study of LEES et al. (1967), the strain gauge in both positions was set at "heart level", while LUCAS et al. (1979) used a catheter-tip strain gauge within the ascending aorta. No postural change in blood pressure was found which proves that the postural change in blood pressure in non-pregnant subjects in only due to a hydrostatic difference.

*4.2.2 Pregnant subjects*

The preceding section 4.1 dealt with factors which may influence the phenomena found due to aortocaval compression in the supine position and the absence of this compression in a lateral position, as e.g. was shown in the treatment of those patients who suffered from the supine hypotensive syndrome.

The heart of a pregnant woman in the last trimester of pregnancy appears to be enlarged, as can be seen on an X-ray. This could be caused by elevation of the diaphragm and increased cardiac output (COOLEY and SCHREIBER, 1968). The rib margins are elevated and flared, thus increasing the transverse diameter of the chest (HYTTEN and LEITCH, 1971). At the same time the diaphragm is elevated and the heart assumes a more transverse position. These anatomic changes tend to increase the physical

TABLE 4.2.2 LEFT LATERAL VERSUS SUPINE POSITION IN LATE PREGNANCY

| Authors | Patients | Methods* | Postural BP differences *** (Δ)mmHg ΔS | ΔD | Remarks |
|---|---|---|---|---|---|
| TROWER and WALTERS (1968) | 14 controls<br>10 1st trim.<br>10 2nd trim.<br>10 3rd trim. | RR** | 15.3<br>17.5<br>13.0<br>10.8 | 15.0<br>16.5<br>17.2<br>14.2 | ΔD greatest in 2nd trimester |
| GINSBURG and DUNCAN (1969) | 16 34 weeks<br>24 34 weeks<br>16 p.partum | Arterial catheter | 5.3<br>7.0<br>-0.7 | 3.8<br>6.1<br>0.6 | Degree of change similar in normotensive and hypertensive subjects |
| SCANLON (1974) | 12 hypert.<br>8 normot.<br>8 p.partum | Ultra-sound | 9<br>8<br>8 | 14<br>13<br>6 | |
| ESKES et al. (1974) | 17 M + P | RR | 14.2 | 15.1 | |
| LIM and WALTERS (1976) | 11 normot.<br>6 hypert. | Modified RR | -4.8<br>-8.0 | +0.1<br>-12.2 | Positional differences not larger in hypertensive subjects |
| HOVINGA et al. (1978) | 7 toxaemic head engaged | Arterial catheter | 7.6 | 3.2 | Conversation more influence than postural change |

* : all prospective cases

** : RR = Riva-Rocci

*** : positive values indicate supine BP > lateral BP
negative values indicate lateral BP > supine BP

distance and consequently the hydrostatic pressure gradient between the right arm and the heart in the left lateral position in pregnant subjects.

The positional blood pressure differences in 17 pregnant women (ESKES et al., 1974) were thought to be caused by hydrostatic factors and partly by baroreceptor reflexes; this suggestion was also put forward by CAMPBELL (1978).
No significant postural blood pressure changes were found in the 8 subjects in late pregnancy of LEES et al. (1967) who recorded the blood pressure intra-arterially with the external strain gauge set at "heart level".
SCANLON (1974) investigated 28 pregnant patients in both supine and lateral positions with an automated ultrasound device, the Arteriosonde$^{R}$ and considered the found blood pressure variations in these different positions as postural differences due to the impossibility to have the brachial, posterior tibial and peroneal arteries in one plane.
LUCAS et al. (1979) measured the distance from the right to the left upper arm in their pregnant subjects and found this distance to be consistent with the expected hydrostatic difference which indicates that there is no increase in the central blood pressure.

Thus, postural blood pressure differences from the left lateral to supine positions (and vice versa) are mainly due to hydrostatic differences.

However, recent studies point to a difference between normotensive and (pre-eclamptic) hypertensive pregnant subjects; the enhanced postural blood pressure differences from the left lateral to the supine position may be used as a prediction of the later development of PIH, the so-called roll-over test (section 6.5).
The authors mentioned in Table 4.1 and 4.2.2 studied postures in pregnancy and most of them found a difference in blood pressure when the position was changed from the left lateral to the supine position, or vice versa.
Intra-arterial blood pressure measurements yielded hardly any

postural changes in blood pressure in the subjects studied by QUILLIGAN and TYLER (1959) and LEES et al. (1967), but small blood pressure changes were observed by GINSBURG and DUNCAN (1969) and HOVINGA et al. (1978). GINSBURG and DUNCAN (1969) found no difference in the degree of change in normotensive and hypertensive subjects. The same results were reported by LIM and WALTERS (1976). HOVINGA et al. (1978) pointed out that conversation had far more influence in blood pressure differences than postural changes.

The blood pressures measured in the left lateral position are found to be lower than those measured in the supine position, with the exception of those subjects described by McROBERTS (1951), QUILLIGAN and TYLER (1959), WRIGHT (1962), GINSBURG and DUNCAN (1969) and LIM and WALTERS (1976). TROWER and WALTERS (1968) found the highest postural change in diastolic blood pressure in the second trimester of pregnancy. This pointed to enhanced local neurovascular reflexes of the brachial arteries.

ESKES et al. (1974) counted the pulse rate in their 17 pregnant subjects and found an increase of pulse rate in 10 out of 17 subjects in the left lateral position, pointing to a better venous filling of the right atrium in this position. Conclusions drawn from this study were that both the hydrostatic differences and the Bainbridge reflex are involved in the lower measured blood pressures in the left lateral position. The influence of the enhanced vascular reactivity and the predictive value of the roll-over test are described in Chapter 6.

### *4.3 Conclusions*

The frequency of the occurrence of the supine hypotensive syndrome is estimated at 0.5% to 12% of all women in late pregnancy, when lying in the supine position during at least two minutes. Compression of the inferior vena cava in the supine position by the gravid uterus causes reduced atrial filling and hence a diminished cardiac output. If the venous return is insufficiently maintained by an underdeveloped collateral venous

system, the symptoms of the supine hypotensive syndrome are likely to occur. Treatment consists of turning the patient to a lateral side.

Due to aortic compression a hypotension in the lower abdomen and legs is noted. Thus, aortocaval compression gives an enhanced femoral venous pressure and a decreased femoral arterial pressure, whereas cranial to the obstruction usually a normal blood pressure is maintained by the baroreceptor reflexes.

Due to the obstruction of the arterial flow to the utero-placental unit, foetal distress sometimes develops.

According to some authors the supine hypotensive syndrome develops less frequently when the foetal head is engaged, than when the head is still floating above the pelvic brim.

Postural blood pressure differences in both non-pregnant and pregnant subjects between the left lateral and supine positions are greatly determined by hydrostatic pressure differences.

From the obstetric point of view some levels of blood pressure are considered to be hypertensive, because above a certain level the perinatal mortality and morbidity are increased. However, the life expectancy in subjects described in actuarial statistics is not necessarily shortened at a blood pressure level at which the infant mortality and morbidity are increased. (FRIEDMAN and NEFF, 1976; PAGE and CHRISTIANSON, 1976a).

## *5.1 Gestational and pre-existing hypertension*

Excellent reviews on the classification and definition of hypertension during pregnancy are given by CHESLEY (1978) and ZUSPAN (1978).
The Committee on Terminology of the American College of Obstetricians and Gynecologists has modified the classification and definitions as issued by the American Committee on Maternal Welfare (DAVIES, 1971; CHESLEY, 1978).

*Gestational hypertension* is defined as a rise in the systolic blood pressure of at least 30 mmHg or a rise in the diastolic blood pressure of at least 15 mmHg, or the presence of a systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg in pregnancy. PAGE (1972; 1976) suggested that the mean arterial pressure (MAP), being the diastolic blood pressure added to one-third of the pulse pressure, should replace the above mentioned definition (MAP>105 mmHg). This formula was developed by BURTON (1965) and advocated by PAGE (1972; 1976) for use as a single figure, expressing the expelling force of the heart against the peripheral resistance. Thus, for example, a blood pressure of 140/90 mmHg is expressed as MAP=107 mmHg.

The classification of hypertension in pregnancy seems best defined by the American Committee on Maternal Welfare (CHESLEY,1978):
A. The disease peculiar to pregnancy
   1. Pre-eclampsia
   2. Eclampsia

B. Diseases independent of pregnancy
   1. Chronic hypertension of whatever cause
C. Pre-eclampsia or eclampsia superimposed upon chronic hypertension or renal disease.
D. Transient hypertension
E. Unclassified hypertensive disorders
F. Recurrent hypertension

*Pre-eclampsia* may be diagnosed if a woman who, when examined early in pregnancy, is found to have a normal blood pressure and no proteinuria, develops hypertension, proteinuria and/or oedema in the third trimester of pregnancy (CHESLEY, 1978).

*Mild pre-eclampsia* is often referred to as pre-eclamptic toxaemia in those patients in whom a recorded diastolic blood pressure of at least 90 mmHg was found "on at least two separate occasions in the last trimester of pregnancy" (GINSBURG and DUNCAN, 1969).

*Eclampsia* is defined as the occurrence of fits in a pre-eclamptic patient.

*Pre-existing, chronic or essential hypertension* is diagnosed by a diastolic blood pressure of more than 90 mmHg at the first antenatal visit (VARMA and CURZEN, 1973) or before 24 weeks of pregnancy on three separate occasions thereafter,antenatally and at the postnatal visit (CHESLEY, 1978).

*Superimposed gestational hypertension* is defined as the situation in which the patient was known to have hypertension before pregnancy or proves to have hypertension after pregnancy due to unknown reasons or due to renal disease (KINCAID-SMITH and FAIRLEY, 1976).

*Transient hypertension* is the gestational hypertension in an otherwise normotensive woman and which disappears soon after delivery.

*Recurrent hypertension* is the hypertension which recurs in subsequent pregnancies; this may be considered as a screening test for the development of hypertension in later life (see section 5.5).

Predisposing factors for the development of pre-eclamptic toxaemia, pre-eclampsia and eclampsia are nulliparity, familial

history of pre-eclampsia, diabetes, multiple gestation; low and high age, pre-existing hypertension, vascular and renal disease, hydatiform mole and poly-hydramnios (MacGILLIVRAY, 1961; CHESLEY, 1978; ZUSPAN, 1978).
Various other factors may modify the course of pre-eclampsia: age and parity (HEADY et al., 1955; VOLLMAN, 1976; CHRISTIANSON, 1976), race (MacGILLIVRAY, 1969 ; VOLLMAN, 1976), short stature (THOMSON et al., 1968) environmental factors, such as diet (protein, salt), socio-economic factors (poverty, ignorance, marriage at young age), weather, climate, season, and most important the lack of medical care (W.H.O., 1965; DAVIES, 1971; VAN DONGEN, 1977; CHESLEY, 1978).

*5.2 Pregnancy outcome as related to hypertension*

The most used parameter to measure the foetal outcome is the perinatal mortality (PNM) which is defined as the death of an infant, occurring before, during or after birth within the period from the end of the 28th week of pregnancy to the end of the 7th day of postnatal life (W.H.O., 1965).
The perinatal mortality rises if the systolic and diastolic blood pressures exceed 140 and 90 mmHg, respectively, or when the systolic blood pressure is lower than 105 mmHg. The found dividing line of 140/90 mmHg is however not strict, because a gradual increase in blood pressure shows also a gradual rise in PNM (McCLURE BROWNE, 1961; see Table 5.2).
The British Mortality Survey in 1958 (BUTLER and ALBERMAN, 1969) yielded a mortality rate of 38 per 1000 total births. This figure rose to 62 per 1000 births in those primiparae over 35 years who developed toxaemia.
The data from the Collaborative Perinatal Project suggest that the PNM rises abruptly, if the diastolic blood pressure exceeds 84 mmHg (FIREDMAN and NEFF, 1976; 1978). A blood pressure rise of more than 5 mmHg (between the 20th and 30th week of pregnancy) is associated with an increased PNM (MacGILLIVRAY, 1961); according to McCLURE BROWNE (1961) this rise is of predictive value if the systolic and diastolic increments exceed 60 and 50 mmHg, respectively.

A pure gestational hypertension gives no increased risk for the foetus (PAGE and CHRISTIANSON, 1976b), whereas hypertension (whatever the cause) in combination with proteinuria scores the highest percentage of PNM (TWEEDIE and MENGERT, 1965; DUNLOP, 1966; TERVILÄ et al., 1973; PAGE and CHRISTIANSON, 1976a, 1976b; FRIEDMAN and NEFF, 1976, 1978, see Table 5.2).

Chronic hypertension predisposes for pre-eclamptic toxaemia (TWEEDIE and MENGERT, 1965). Many patients with the diagnosis of pre-eclampsia proved to have renal diseases, and the pre-eclampsia was superimposed (KINCAID-SMITH and FAIRLEY, 1976; CHESLEY, 1978).

TERVILÄ et al. (1973) found the systolic blood pressure of more predictive value than the diastolic blood pressure in contrast with most authors mentioned in Table 5.2.

The largest numbers of patients are given by FRIEDMAN and NEFF (1976, 1978). Their material comes from 12 clinics and is pooled into a collaborative study. Nearly 40.000 gravidae were seen and many variables recorded. The conclusion from their studies was , although only 11% of the subjects were classified as hypertensive, that these women accounted for as much as 25% of the perinatal mortality. The black women in the U.S.A. are more liable to get an increase in PNM and growth retarded infants, consequently also higher morbidity (PAGE and CHRISTIANSON, 1976a, 1976b; FRIEDMAN and NEFF, 1976, 1978).

Foetal growth retardation or poor intrauterine foetal growth or dysmaturity is the phenomenon that a child in utero or after birth has a birth weight that is considered to be too low for a given gestational age in a certain population. Statistically a birth weight below the mean minus two standard deviations (<2.3 percentile) may be considered as a real value of growth retardation (GRUENWALD, 1963). For practical reasons, however, most people define the poor intrauterine foetal growth as a weight below the 10th percentile (LUBCHENCO et al., 1963; THOMSON et al., 1968; KLOOSTERMAN, 1973; ZOLTAN, 1977), but the Collaborative Perinatal Project (FRIEDMAN and NEFF, 1976, 1978) considers the 5th percentile as a good parameter.
This condition is important because of the association with high

TABLE 5.2 PERINATAL MORTALITY (PNM)

| Authors | Patients | PNM* | Remarks |
|---|---|---|---|
| McCLURE BROWNE (1961) | 7344 P | Over 30 years and with prot.: 117 | Syst.BP>140: PNM↑<br>Diast.BP>90: PNM↑<br>Syst.BP<105: PNM↑ |
| Mac-GILLIVRAY (1961) | 4215 P | 57.5 | PNM with excessive BP↑ and weight gain between 20th-30th week. |
| TWEEDIE and MENGERT (1965) | 368 chronic hypert.<br>71 superimposed toxaemia<br>439 total | 60<br>211<br>84 | Chronic hypertension predisposes to pre-eclamptic toxaemia. |
| DUNLOP (1966) | 1182 | Mild chr.hypert. 26<br>severe chr. hypertension 183<br>Mild pre-eclampsia 41<br>severe pre-ecl. 270 | |
| BUTLER and ALBERMAN (1969) | 17204 P + M | 38 primiparae over 35 years with toxaemia: 62 | One week survey of all births in the United Kingdom (1958) |
| TERVILÄ et al. (1973) | 4404 EPH-gestosis | mild 51<br>severe 100 | Syst.BP more predictive than diastolic BP; worst prognosis with hypertension and proteinuria. |
| PAGE and CHRISTIANSON (1976a) | 14833 P + M | MAP 2<85 : 32.7<br>MAP 2≥85 : 49.5 | If MAP 2>85 mmHg ; PNM↑, PIFG↑; blacks more affected than whites |
| PAGE and CHRISTIANSON (1976b) | 12954 P + M | MAP 3≥105 mmHg<br>No prot. prot.<br>Whites 36.9 95.2<br>Blacks 63.4 250 | Blacks more affected than whites in PNM, PIFG and morbidity |
| FRIEDMAN and NEFF (1976;1978) | 36636 P + M | Hypert.only 104<br>Hypert.+prot.147<br>Low diast.BP 44 | 11.4‰ of group is hypertensive, but accounted for 25.1% of PNM |

* : rate per 1000 births

P, primigravidae; M, multigravidae; MAP 2, mean arterial pressure in the second trimester; MAP 3, in the third trimester; PIFG, poor intrauterine foetal growth.

perinatal mortality, enhanced morbidity (defined as a poor condition at birth or in the nursery, with survival), high risk for congenital anomalies and impaired development during childhood (GRUENWALD, 1963; VAN DEN BERG and YERUSHALMY, 1966; THOMSON et al., 1968; TERVILÄ et al., 1973; WEHMER and HAFEZ, 1975; PAGE and CHRISTIANSON, 1976b). In a group of 2400 consecutive pregnancies in which the hypertensive disease gave rise to a "small-for-date" child the PNM was as high as 53‰. Twin pregnancies and congenital malformations as a cause for severe growth retardation in the same group of pregnant subjects scored a PNM of 42‰ and 38‰, respectively (GRUENWALD, 1963).

The incidence of both the PNM and "small-for-dates" infants was found to increase sharply at a systolic blood pressure of 175 and a diastolic blood pressure of 115 mmHg; making it worse if proteinuria was detected (TERVILÄ et al., 1973).

Chronic hypertension without superimposed toxaemia is responsible for an increased PNM rate and an increased incidence of PIFG (TWEEDIE and MENGERT, 1965; ARIAS, 195).

DE JONG (1975) demonstrated that both nulliparae and multiparae with rising diastolic blood pressures delivered more children with non-optimal neurologic conditions than those who had stable diastolic blood pressures. The neurologic condition was assessed with the method of Prechtl and Beintema.

### *5.3 Placental abruption*

It has been demonstrated that no relationship exists between the occurrence of placental abruption and mild toxaemia. The frequency, however, is ten-fold in superimposed and severe toxaemia, suggesting that pre-existing damaged arterioles are the primary cause of abruptio placentae (KLOOSTERMAN, 1962; DROGENDIJK, 1967).

The inferior vena cava is compressed by the gravid uterus when the woman in late pregnancy lies in the supine position. This causes a higher venous pressure in the lower abdomen and femoral veins. In some cases premature separation of the placenta is reported in the normally implanted placenta in patients who developed a

supine hypotensive syndrome. LEMTIS and SEGER (1974c) described two patients who developed supine hypotensive syndrome, followed by placental abruption. However, both placentae were inserted in the uterine fundus and showed difficulties in separation. Serious vascular placental anomalies were found in both placentae, again suggesting that the damaged or changed arterioles are the reason for placental abruption.

### *5.4 Prediction of hypertension during pregnancy*

In section 5.1 a classification of hypertensive diseases in pregnancy was described. Pregnancy induced hypertension (PIH) may be defined as the development of hypertension after the 24th week of pregnancy and is associated with oedema, weight gain and usually proteinuria; this definition fits pre-eclamptic toxaemia (ZUSPAN, 1978).
However, the superimposed hypertension is far more dangerous for both mother and child and should be carefully looked for (subsections 5.2 and 5.5).

It has been stated by McCLURE BROWNE (1961) that the higher the initial blood pressure during pregnancy in women over 30 years, the more likely the blood pressure will be increased during pregnancy.

MacGILLIVRAY (1961) showed in an epidemiological study that if in first pregnancies the diastolic blood pressure by the 20th week rises above 80 mmHg or by the 30th week above 90 mmHg, the woman is likely to develop pre-eclamptic toxaemia.

GALLERY et al. (1977) demonstrated that 67 normotensive gravidae had significantly higher casual blood pressures than when measured under standardized conditions, irrespective of posture. However, the 15 patients who developed hypertension in late pregnancy showed no differences in diastolic blood pressures when the casual and basal readings were compared. It was concluded that measurements under standardized conditions might predict a PIH because this phenomenon was already present at the time of 17-20 weeks of gestation. In fact, the patients who developed hypertension in late pregnancy did not show a mid-

pregnancy dip. The phenomenon of the mid-pregnancy dip has been discussed in section 3.3.

PAGE and CHRISTIANSON (1976a) calculated the mean arterial pressure in the second trimester of pregnancy (MAP 2), and found a significant increase of the occurrence of hypertension, proteinuria and pre-eclamptic toxaemia if the MAP 2 exceeded 90 mmHg (see Table 4.2).

PHELAN (1977) could enhance the prediction of the development of PIH in 97 primigravidae in combining this predictive value of the MAP 2 with the results of the "roll-over" test (see Table 6.5). With a positive "roll-over" test of a MAP 2>85 mmHg a correct prediction was made in 29% and 47%, respectively; with the two items together this prediction rose to 88%.

A familial tendency to develop pre-eclamptic toxaemia and eclampsia was described by MacGILLIVRAY (1961) and CHESLEY et al. (1961, 1968) and CHESLEY (1978). CHESLEY et al. (1961) studied the occurrence of hypertensive disorders of pregnancy in sisters, daughters, granddaughters and daughters-in-law of women who had had eclampsia and found a strong familial tendency. The prediction of development of pregnancy induced hypertension in later pregnancy by means of the "roll-over" test is described in section 6.5.

### *5.5 Remote prognosis*

Maternal mortality rate is defined as the number of deaths per 1000 deliveries, comprising all deaths of women during pregnancy, in childbirth and puerperium (W.H.O., 1965).

TWEEDIE and MENGERT (1965) found that 3‰ of maternal deaths were caused solely by chronic hypertension in pregnancy and CHESLEY (1978) 0.9‰, whereas the deaths due to superimposed pre-eclamptic toxaemia rose to 14 and 10‰, respectively.

A gradual increase in both the PNM and the maternal mortality rates has been described from mild pre-eclampsia, uncomplicated chronic hypertension, severe pre-eclampsia to superimposed pre-eclamptic toxaemia (TWEEDIE and MENGERT, 1965; CHESLEY, 1978).

As pregnancy itself does not cause chronic hypertension, it is

clear that a higher blood pressure in pregnancy, whatever the cause, is predictive for a higher chance of persistent hypertension in later life (JULIUS and SCHORK, 1971; BENGTSSON and LINDQUIST, 1976; ROBERTS and PERLOFF, 1977). Transient and recurrent hypertension may be considered as a screening test for the development of hypertension in later life. Especially the recurrent hypertension may unmask chronic hypertension (CHESLEY and SLOAN, 1964; PAGE and CHRISTIANSON, 1976b; ROBERTS and PERLOFF, 1977).

Repeated hypertensive pregnancies do not cause chronic hypertension in women, but rather are a sign of antecedent hypertension or renovascular disease (MASTBOOM, 1949; CHESLEY et al., 1968, 1976; CHESLEY, 1978). McCARTNEY (1969), and KINCAID-SMITH and FAIRLEY (1976) reported that patients with a clinical diagnosis of pre-eclampsia proved to have in respectively 25% and 38% of cases renal lesions not consistent with pre-eclampsia, as was seen in renal biopsies performed during pregnancy. In the follow-up studies of CHESLEY et al. (1968), CHESLEY (1976a) and CHESLEY et al. (1976), in women who were treated for eclampsia between 1931 and 1951, it has been made very clear that eclampsia in the first pregnancy does not enhance the prevalence of hypertension or death due to hypertensive complications in later life, but a considerable increase of hypertension and death is seen in multiparous women, indicating a pre-existing vascular or renal disease before their eclamptic fits.

BENGTSSON and LINDQUIST (1976) found in their population study of 1462 women between the ages of 38 - 60 years 126 hypertensive subjects. Significantly more hypertensive subjects (48%) reported a history of hypertension and/or proteinuria during preceding pregnancies than the normotensive subjects (16%).

### *5.6 Conclusions*

Pregnancy induced hypertension is hypertension during pregnancy developing in an otherwise normotensive woman and disappearing soon after delivery. It occurs mainly in the first pregnancy. Other predisposing factors are multiple gestation, low and high age, diabetes, poly-hydramnios.

Pre-existing hypertension, vascular and renal diseases greatly influence the course of blood pressure during pregnancy and the foetal outcome.

The perinatal mortality rises with increasing blood pressures, especially with the diastolic blood pressures. A dividing point may be laid at 85 mmHg diastolic blood pressure. However, no specifications of postures, Korotkow sounds, or standardization in the procedures of blood pressure estimation are given. Hypertension with proteinuria gives higher perinatal mortality rates.

Chronic hypertensive women who develop pre-eclampsia score the highest figures in perinatal mortality.

Unsatisfactory socio-economic factors predispose to poor foetal outcome.

Foetal growth retardation occurs more readily in hypertensive patients as compared with normotensive subjects. These small-for-dates infants also show a higher perinatal mortality and morbidity.

Thus, chronic hypertension has an adverse effect on the foetal outcome, but mild gestational hypertension does not.

Placental abruption occurs mainly in those patients with damaged or aberrant arterioles in the placenta.

Estimation of resting blood pressures (see glossary of terms) during pregnancy may predict the development of hypertension later in pregnancy by the absence of a mid-pregnancy dip.

The increased vascular reactivity in pre-eclampsia could be the explanation that this mid-pregnancy dip is absent in patients who develop pregnancy induced hypertension (MacGILLIVRAY, 1961; GALLERY et al., 1977). However, an exaggerated decrease in blood pressure was observed in hypertensive women during pregnancy by CHESLEY and ANNITO (1947), BROWNE (1947), MORRIS (1958) and TOWNSEND (1959). The foetal prognosis is considered to be better if a clear mid-pregnancy drop develops (CHESLEY, 1978).

Hypertension in pregnancy does not cause chronic hypertension in later life. However, repeated hypertensive pregnancies are often a sign of the development of hypertension in later life due to underlying disease in the patient.

The prognosis for women with superimposed pre-eclamptic toxaemia is significantly poorer when compared with the normotensive and mild gestational hypertensive subjects.

Hypertension is the principal sign in detecting pre-eclamptic toxaemia. The systolic blood pressure reflects the change in cardiac output and the diastolic blood pressure reflects the changes in the pre-capillary arterioles. The blood pressure can rise either by an increase in the cardiac output or by an augmentation of the systemic vascular resistance (see section 2.1).

Ten normotensive and ten pre-eclamptic patients in late pregnancy were studied by ASSALI et al. (1964). The levels of the blood pressures were obviously higher in the pre-eclamptic group than in the normotensive group. The cardiac output, however, determined with a dye dilution technique, proved to be essentially the same in the two groups, with 6.3 and 6.1 l/min in the pre-eclamptic and normotensive subjects, respectively. Thus the calculated systemic vascular resistance in the pre-eclamptic patients was higher than in normotensive patients (see equation in section 2.1).

An autonomic blockade by tetraethylammonium chloride (TEAC) and a selective spinal anaesthetic at the 4th cervical level was made in non-pregnant and pregnant normotensive, hypertensive and pre-eclamptic subjects in the supine position (BRUST et al., 1948; ASSALI and PRYSTOWSKY, 1950). All non-pregnant subjects showed no effect from the blockade, but both the normotensive and hypertensive pregnant patients reacted with a severe hypotension, whereas the pre-eclamptic patients did not. If the legs were held at an angle of 90$^{o}$ or the patient put on her left side, the hypotension was less. It was concluded that the venous pooling in the legs, mainly due to compression of the gravid uterus on the inferior vena cava was the reason for this hypotension; that in normal pregnancy the blood pressure is largely maintained by neurogenic tone, but that in pre-eclamptic patients the vascular tone was maintained by non-neurogenic mechanisms.

DUNCAN et al. (1968) measured plethysmographically the blood flow in the forearm of 31 pregnant normotensive and 39 chronic hypertensive pre-eclamptic women after arterial occlusion and local exercise. They found increased vascular resistance in pre-eclamptic subjects as compared with normotensive women.

One may suggest an inappropriate vasodilatation either because of failure to respond to normal influences (e.g. abnormal vessel wall, DUNCAN et al., 1968) or vascular hyperresponsiveness to circulating substances.

### *6.1 Epinephrine and norepinephrine*

RAAB et al. (1956) infused epinephrine and norepinephrine in 163 normotensive pregnant subjects between the 28th and 34th week of gestation. The rise in blood pressure of the 100 subjects who remained normotensive throughout pregnancy was significantly less than that of those who later developed hypertensive disease in the same pregnancy.

ZUSPAN et al. (1964) reported that 9 pre-eclamptic and 4 hypertensive women reacted to epinephrine and norepinephrine infusions with greater systolic blood pressure responses than 7 normotensive pregnant subjects.

TALLEDO et al. (1968) studied 13 hypertensive patients in the third trimester of pregnancy and found that the seven pre-eclamptic patients showed increased sensitivity to infused AII and norepinephrine in contrast with the 5 chronic hypertensive patients.

POLAND and LUCAS (1979) found lower plasma levels of epinephrine and norepinephrine between the 28th - 32nd week of gestation, and higher levels between the 36th - 40th week in 6 primiparous women, who subsequently developed hypertension, as compared with 17 normotensive pregnant control subjects.

### *6.2 Dehydroisoandrosterone sulfate (DS)*

Profound vasospasm is one of the features of pre-eclampsia and may be considered as the cause of reduction in the utero-placental blood flow, resulting in decreased maternal placental

perfusion (GANT et al., 1971; WORLEY et al., 1978).

The metabolic clearance rate of dehydroisoandrosterone sulfate (MCR-DS) is defined as the volume of plasma which is cleared of DS per unit of time. DS, in late pregnancy mainly produced by the foetal adrenals, is the principal precursor of placental oestriol synthesis.

In normotensive human pregnancy the MCR-DS increases continuously, as was demonstrated by administering labeled DS in primigravid and multiparous women. In those primigravidae who ultimately developed PIH, a higher MCR-DS was found till 3 - 4 weeks prior to the evidence of the disease; at this time a drop occurred, reaching levels as in normal pregnancy. If the pregnancy was continued, this decrease continued and eventually reached non-pregnant levels. Pregnant hypertensive patients showed the similar pattern. It was concluded that this decreased MCR-DS represented a decrease in utero-placental blood flow. Interestingly, administration of diuretics or antihypertensive drugs and salt restriction enhanced this decrease in MCR-DS (GANT et al., 1971; GANT et al., 1976; WORLEY et al., 1978).

The pressor response to infused angiotensin II was determined (GANT et al., 1971) in those primigravid subjects who showed a constant rise in the MCR-DS and thus developed no pre-eclampsia. At about the 20th week of gestation they became resistant to the pressor effects of AII and remained resistant until delivery. The primigravid patients who showed a decreasing MCR-DS 3 to 4 weeks prior to the development of clinical pre-eclampsia, exhibited an enhanced responsiveness to the effect of infused AII. This sensitivity was detected as early as the 22nd week of gestation

### *6.3 Angiotension II (AII)*

ABDUL-KARIM and ASSALI demonstrated in 1961 that increased amounts of infused AII were needed in normotensive pregnant women to obtain a pressor response when compared with non-pregnant subjects.

CHESLEY et al. (1965) found that on the average 2.6 times as

much AII was needed to cause a rise in blood pressure in normotensive pregnant women as compared with non-pregnant subjects. TALLEDO et al. (1966) infused AII in 15 normotensive and 9 pre-eclamptic women and found for normotensive subjects the same results as CHESLEY et al. had described in 1965 but pre-eclamptic women proved to be more sensitive to AII, i.e. less AII was required to raise the diastolic blood pressure by 20 mmHg. The findings of TALLEDO et al. (1968) in 7 pre-eclamptic subjects were essentially the same as those described in 1966 (TALLEDO et al., 1966).

GANT et al. (1973) showed that the refractoriness to AII, characteristic of normal pregnancies, was lost as early as the 26th week of pregnancy in 72 young primigravidae who later developed PIH. Patients who required more than 8 ng/kg/min of AII remained normotensive, in contrast to those who required less than this amount; 90% of them developed PIH.

Renin, aldosterone and angiotensin II levels are increased in normal pregnancy when compared with non-pregnant women; however, patients with pre-eclamptic toxaemia have lower levels than normotensive pregnant subjects (BROWN et al., 1963; WEIR et al., 1973; GORDON et al., 1973).
It is not the level of circulating renin, aldosterone and AII that is responsible for the hypertension but the difference in sensitivity of the resistance and capacitance vessels to the vasoconstrictor effect of AII (GORDON et al., 1973; GANT et al., 1973; GANT et al., 1974a; 1974b).
In their elegant study of 10 non-pregnant and 19 pregnant women near term GANT et al. (1974a) showed that after rapid infusions of normal saline the decrease in a volume deficit in normotensive pregnant subjects and the decrease in the plasma renin level did not indicate an altered pressor responsiveness to exogenously administered AII, suggesting that the vessel resistance to AII is indeed the factor. However, in 9 normotensive pregnant subjects near term a hypertonic saline solution was given and it was clear that the refactoriness to AII was suddenly diministed, providing evidence that vascular intracellular sodium could change the pressor response.
This phenomenon is also described by PAGE (1972) and GOECKE (1979).

TALLEDO et al. (1966) suggested that in toxaemic patients lower progesterone levels are found; these low levels would cause a diminished production of aldosterone because of lower levels of AII, resulting in an increased vascular reactivity to exogenous AII.

MATI et al. (1971) described 21 rabbits who were treated with daily progesterone injections (2.5 mg/kg body weight); all developed hypertension. Administration of prolactin, however, together with the progesterone, resulted in a lowering of the blood pressure within 2 days. It was concluded that the vessel wall itself affected the vascular sensitivity because prolactin could also prevent the development of hypertension, if it was administered with the progesterone from the start.

Five subjects who were angiotensin-sensitive and already had a mild PIH in the 37th - 40th week of gestation, were infused with progesterone but no change was found. However, infusion of 5α-dehydroprogesterone in 7 subjects with PIH and increased AII sensitivity resulted in prompt restoration of vascular resistance (EVERETT et al., 1978a). It is suggested that progesterone or its metabolites are perhaps necessary to maintain the blood pressure during pregnancy. It is notable that progesterone has a natriuretic effect (KAULHAUSEN et al., 1979)

The utero-placental blood flow in normal late pregnancy is tremendously increased, but the vasoconstrictor effect of epinephrine, norepinephrine and AII is decreased (see sections 6.1 and 6.3). As the AII level is associated with an increase in uterine blood flow, results suggest that PG of the E-series can antagonize the vasopressor effect of AII (McGIFF et al., 1970; LONIGRO et al., 1973; SPEROFF, 1973; TERRAGNO et al., 1976). Locally produced PGE's are known to be potent dilators in many vascular beds (BRODY and KADOWITZ, 1974) and thus prostaglandins may play an important role in maintaining blood flow to organs demonstrating a high rate of prostaglandin synthesis. If a reduced utero-placental flow occurs, for example due to

enhanced intrauterine pressure, the uterus starts producing more renin and thus higher AII levels appear. The peripheral resistance is increased, but the flow to the uterus is enhanced, most problaby by local trophoblast prostaglandin production, stimulated by the increased AII levels (SPEROFF, 1973).
The blood flow through the utero-placental unit is reduced in toxaemic patients, as was shown by GANT et al. (1976) and WORLEY et al. (1978) (see section 6.2). RYAN et al. (1969) extracted a vasodepressor agent from 8 placentae which had the properties of PGE. More of this substance was found in the placentae of four normotensive than in the placentae of four toxaemic subjects. The agents produced a large fall in the blood pressure of normotensive animals.

SPEROFF et al. (1977), after administration of the prostaglandin synthetase inhibitor indomethacine to monkeys, demonstrated that the blood pressure response to infused AII was enhanced and the increase of uterine blood flow inhibited, suggesting that prostaglandins can mediate the effects of AII. The same results were found in dogs by CLARK et al. (1977). Another prostaglandin synthetase inhibitor, meclofenomate, was infused and a significant decrease in PGE level in uterine vein plasma was found, in combination with increased vascular resistance of the uterine vessels. Thus, inhibition of prostaglandin synthesis alters vasoconstrictor response.
The effective pressor dose of AII before indomethacin administration in 5 normotensive women was 13.2 ng/kg/min, but after indomethacin administration only 5.8 ng/kg/min was required to produce the same rise in the diastolic blood pressure of 20 mmHg (EVERETT et al., 1978a).
In yet another experiment by EVERETT et al. (1978b) in 11 normotensive pregnant women the administration of indomethacin resulted in a decrease in required AII from 20.2 to 7.9 ng/kg/min. In three women, treated with aspirin, the same results were reported.

### *6.5 Roll-over test*

GANT et al. (1973) showed an enhanced reaction to infused AII

in 72 primigravidae who developed PIH later in pregnancy (see section 6.3). The same patients also had an exaggerated blood pressure response when turned from the left lateral to the supine position.

GANT et al. (1974b) described a simple clinical test, the "roll-over" test, which they felt identified those patients at high risk for the development of hypertension in late pregnancy. The test was performed on 30 normotensive primigravidae between 28 and 32 weeks of pregnancy. A base line resting blood pressure was obtained with the subject in the left lateral recumbent position. Then, she was turned to the supine position, and the blood pressure measurements were repeated immediately and after five minutes. A rise of more than 20 mmHg in the diastolic blood pressure was considered to be an abnormal or positive response. 93% Of GANT's pregnant subjects who exhibited a rise in diastolic blood pressure of more than 20 mmHg during this roll-over test subsequently developed hypertension, compared with a rate of only 9% in the gravidae with a negative test (see Table 6.5). The last columns of Table 6.5 give the percentage of subjects (with positive and negative tests respectively) who developed pregnancy induced hypertension.

This test was called the "supine pressor test" by GANT et al. (1974b), but GUSDON et al. (1977) were the first people to give tha name "roll-over test" to this manoeuvre (ROT). In their prospective study of 60 primigravidae and 60 multiparae between the 28th to 32nd week of pregnancy the same procedure was followed as in the study of GANT et al. (1974b). The predictive value for primigravidae was 50% and for multiparae only 25%, if a positive test was found, whereas the negative test scored far better (see Table 6.5). The results were quite different from those that were seen in the study of GANT et al. (1974b). The explanation for this fact, according to GUSDON et al. (1977), could lie in the groups. Their patients were recruted from a low-risk group (high socio-economic level) in comparison with the high-risk group (low socio-economic level) of GANT et al.(1974b).

The prospective study of KARBHARI et al. (1977) included 178 primigravidae from the low socio-economic groups. The test was called "the supine hypertensive test". The same procedure was followed as given by GANT et al. (1974b). The results were

TABLE 6.5 ROLL-OVER TEST : SUMMARY OF FINDINGS

All studies were performed between 28th and 32nd week of gestation, were prospective and cross-sectional, the Riva-Rocci method was used, Korotkow V sound taken as end-diastolic pressure and the $\chi^2$-test used (*$p<0.05$),if not stated otherwise.

| Authors | Patients | Methods | Patients with Pos. test | Patients with Neg. test | Predictive value for P.I.H. Positive | Predictive value for P.I.H. Negative |
|---|---|---|---|---|---|---|
| GANT et al. (1974) | 30 P | | 16 | 22 | 15(93%)* | 2(9%) |
| GUSDON et al. (1977) | 60 P | | 20 | 40 | 10(50%)* | 3(7%) |
| | 60 M | | 12 | 48 | 3(25%)* | 3(6%) |
| KARBHARI et al. (1977) | 178 P | | 29 | 149 | 27(93%)* | 11(7%) |
| DIDOLKAR et al. (1977) | 51 P<br>34 M | 28-37 weeks | 20 | 65 | 3(15%) | 13(21%) |
| MARSHALL and NEWMAN (1977) | 100 P | | 25 | 75 | 21(84%)* | 7(10%) |
| PHELAN et al. (1977) | 207 P | | 54 | 153 | 21(39%)* | 6(4%) |
| PHELAN (1977) | 97 P | MAP 2+ROT (see text) | 45 | 52 | 13(29%) | 13(25%) |
| O'GRADY et al. (1977) | 24 P | 27-35 weeks serial,Ultra-sound | see text | | See text ; positive test not predictive | |
| THOMPSON and MUELLER-HEUBACH (1978) | 62 P | Applied preventive measures with pos.test (see text) | 28 | 34 | 4(14%)* | 2(6%) |
| CAMPBELL (1978) | 85 P | LSHS K IV | see text | | See text ; no predictive value | |
| POLAND et al. (1979) | 139 P | | 55 | 84 | 24(43%) | 36(42%) |

almost the same (see Table 6.5).

DIDOLKAR et al. (1977) studied prospectively 85 patients, divided into 51 primigravidae and 34 multiparae. However, the results were combined for both groups and the gestational age was between the 28th to 37th week of gestation. The same procedure was followed as described by GANT et al. (1974b), with additional standardization of a balanced diet and one day hospital bedrest. No predictability was found, as is shown in Table 6.5. Actually, 40% of those patients who developed pregnancy induced hypertension (PIH), showed a decrease in blood pressure in the supine position.

MARSHALL and NEWMAN (1977) obtained in a prospective survey of 100 primigravidae the same results as GANT et al. (1974b). The same procedure in "rolling-over" was followed (see Table 6.5).

O'GRADY et al. (1977) performed weekly "roll-over"tests in 24 primigravidae in the age range of 14 to 20 years from the 27th to 35th week of pregnancy. An automated ultrasound technique was used (see section 1.2.2.2). The subjects were placed in the left lateral position and blood pressures were recorded every five minutes for half an hour. The mean of the 7 values was considered as the best approximation of the blood pressure. When the subject was turned to the supine position, the blood pressure was recorded after one and five minutes and the greater value of the blood pressure was considered to represent the real blood pressure value. Only 7 out of the 24 subjects (29%) showed consistent test results. Six subjects had continuously negative "roll-over" tests, as defined by GANT et al. (1974b), and they remained normotensive throughout pregnancy and gave birth to children of normal weight. Only one subject had continuously positive tests, but developed neither PIH nor delivered a small-for-date child. The individual variability between test pairs of one week apart proved to be constant in only 72% of the blood pressure recordings, whereas three and four weeks'intervals were only consistent in 57% and 44% of the recordings, respectively. Most tests (78%) were appreciated as negative "roll-over" tests. The three patients who developed PIH showed alternately positive and negative tests. It was concluded from this serial study that persistently negative tests have predictive value.

PHELAN et al. (1977) studied prospectively 207 nulliparous

pregnant women between the 28th to 32nd week of gestation under the same conditions as those in the study of GANT et al. (1974b). Only 39% of those who showed a positive supine pressor test developed PIH in late pregnancy in contrast with 4% of those with negative tests results.

In section 5.2.3 it has been already stated that the MAP 2, in combination with the roll-over test, predicted more accurately the development of PIH later in pregnancy (PHELAN, 1977).

THOMPSON and MUELLER-HEUBACH (1978) reviewed the literature concerning the "roll-over" test. They concluded that a positive roll-over test had a predictive value of 65% as to the development of PIH in late pregnancy, whereas only 7% with a negative test shared the same fate. In their own investigations, of 62 primigravidae who were "rolled over", those who showed a positive roll-over test were advised to reduce their work and to take additional rest. More protein and less salt intake was also advised. They claimed that due to this advice only 4 (14%) of those who had a positive ROT and 2 (6%) with a negative test developed PIH (see Table 6.5). The difference in the occurrence of PIH between the total group, as referred to above, and their own group was significantly altered ($\chi^2$ test; $p<0.01$). They concluded that the preventive measures of more rest and proper nutrition had suppressed the occurrence of PIH.

CAMPBELL (1978) performed the "roll-over"test in 85 primigravidae at the 30th week of pregnancy. However, the conditions of measurements were different from those used by GANT et al. (1974b). The differences in this study were that all the blood pressures were recorded using the London School of Hygiene Sphygmomanometer and that the diastolic blood pressure was estimated at phase IV rather than phase V.
Preliminary results in 20 normotensive gravidae showed that the mean postural differences in systolic and diastolic blood pressures were 3 to 4 and 5 mmHg respectively. Only three patients in the 85 subjects showed a positional difference in diastolic blood pressure of more than 20 mmHg. No significant differences between the 40 subjects who remained normotensive and the 45 who developed PIH, were found as to the predictive value of the

modified "roll-over" test.

POLAND et al. (1979) demonstrated in their prospective study of 139 primigravidae between the 28th and 32nd week of gestation, that 43% of the subjects with a positive "roll-over" test and 42% with a negative "roll-over" test developed PIH later on in pregnancy. They concluded that the "roll-over" test failed to predict a development of PIH later in pregnancy.

### *6.6. Conclusions*

Vascular reactivity in normal and chronic hypertensive pregnancy is decreased.

However, patients with (superimposed) pre-eclamptic toxaemia or PIH exhibit an enhanced vascular reactivity to pharmacologic stimuli, such as adrenaline, noradenaline and AII.

Vasoconstriction is the pathological phenomenon related to PIH, resulting in decreased uterine blood flow.

Prostaglandins may play an important role; in toxaemic patients the production of prostaglandin E (PGE) is less than in normotensive subjects, leading to an enhanced utero-placental vasoconstriction.

The prediction of the "roll-over" test as to the development of PIH later on in pregnancy identifies to some extent an increased risk for hypertension during pregnancy. The negative test, however, has more predictive value.

The supine position could be one of the stimuli of an augmented vascular responsiveness.

# PART II

## OWN INVESTIGATIONS

## 7.1 Measurements

### 7.1.1 Anamnestic data

When a subject was taken into any of the study groups, and before actual blood pressure measurements were carried out, data concerning pre-existing diseases or former pregnancies were noted according to the following definitions and categories.

Pre-existing hypertension: hypertension found previously in the non-pregnant state:

a. Blood pressure 140/90 mmHg or greater reported by a referring physician or recorded during a previous visit to the hospital clinics, or
b. Patient denied regular life or health insurance, or not permitted full participation in sports on the grounds of elevated blood pressure.

In addition, if hypertension had not been found before pregnancy, but the casual diastolic blood pressure at the first antenatal visit prior to 12 weeks was higher than 90 mmHg in the supine position after two measurements, the subject was also considered to have hypertension predating pregnancy.

Renal disease: in the non-pregnant state, parenchymal renal disease or recurring urinary tract infections.

*In former pregnancies*

- Renal disease: disturbed renal function tests, albuminuria, recurring urinary tract infections.

- Hypertension: diastolic blood pressure exceeding 90 mmHg in supine position (auscultatory method).
- Diabetes gravidarum: treated during pregnancy with carbohydrate enriched, sodium restricted diet and insulin for such indications as poor obstetric history, familial diabetes mellitus, large-for-dates children,abnormal or borderline glucose tolerance tests; but not treated in non-pregnant state with insulin (STOOT, 1978).
- Toxaemia:
  1. diastolic blood pressure (auscultatory method, supine position) exceeding 90 mmHg,
  2. and weight gain more than 500 g/week in the last trimester of pregnancy,
  3. and/or serum uric acid level above normal values (<36 weeks: <330 µmol/l; >36 weeks <450 µmol/l)
- Pre-eclampsia: toxaemia with
  1. proteinuria (>150 mg/24 hrs)
  2. sudden increase of blood pressure and weight (oedema),
  3. signs of vasospasm (visual disturbances, paraesthesias, frontal headache, epigastric pain),
  4. hyperreflexia.
- Eclampsia: convulsions, coma, or both in association with hypertension, proteinuria and oedema. Other reasons for convulsions must be excluded.
- Placental abruption: total and partial.
- Growth retardation: birth weight of an infant below the 10th percentile for the Dutch population (KLOOSTERMAN, 1973). (Synonyms: small-for-dates, small for gestational age (SGA), poor intrauterine foetal growth (PIFG), dysmature (dysmaturity), growth retarded infant).
- Placental infarcts: diagnosed by macroscopic or microscopic examination of the placenta.
- Abortion: expulsion of pregnancy products before the 16th week of pregnancy.
- Immature delivery: delivery of a foetus between 15 and 27 completed weeks of pregnancy.
- Premature delivery: delivery of an infant between 27 and 37

completed weeks of pregnancy.

- Term delivery: delivery of an infant between 37 and 41 completed weeks of pregnancy.
- Post term delivery: delivery of an infant after 41 completed weeks of pregnancy.

*7.1.2 Clinical observations during the pregnancy studied*

- Pregnancy: number includes abortions and ectopic pregnancies.
- Parity: indicates the number of infants born after 15 completed weeks of pregnancy.
- Amenorrhoea: 1. Time which elapsed after the last menstrual period, but only if the cycle was regular (26-32 days);
  2. If the cycle was irregular, a correction was made according to the basal body temperature chart and/or the crown-rump length of the foetus (Ultrasound B-scan) between 6 and 12 weeks conceptional age.
- Height: in cm, as obtained at the first antenatal physical examination.
- Weight: in kg, as obtained on the same day as the blood pressure recording without shoes but with normal clothing.
- Quetelet's Index (Q.I.) (obesity index):
  $\frac{\text{Weight}}{\text{Height}^2}$ kg/cm$^2$ (KHOSLA and LOWE, 1967)
- Renal disease
- Diabetes gravidarum
- Toxaemia
- Pre-eclampsia
- Eclampsia
- Hypertension
- Placental abruption

  } See section 7.1.1

- Excessive weight gain: more than 500 g/week in any period.
- Oedema: generalized oedema; oedema of lower legs and ankles only was not included in this category.
- Proteinuria: >150 mg/24 hrs.
- Negative discongruency: growth retardation of at least two

weeks as assessed by clinical judgement (fundal height) and/or by ultrasound measurements of the biparietal diameter.
- Positive discongruency: fundal height and biparietal diameter more than two weeks ahead of expected size.
- Diet: sodium restricted diet ( < 20 mmol/24 hrs), or carbohydrate enriched diet, alone or in combination.
- Bed rest: out of bed only to make toilet.

*7.1.3 Blood pressure measurements*

- Casual blood pressure measurements were performed in the supine position. A standard mercury sphygmomanometer was used (Erkameter 300, cuff 12 x 23 cm). The fifth Korotkow sound was taken to represent diastolic blood pressure.
- Basal blood pressures were taken with an ultrasound device.

The test was performed as follows: the participant was placed in the supine position and the blood pressure was measured in the right upper arm with an automated ultrasound device, the Arteriosonde$^{R}$ (Roche Medical Electronics Division, Hoffmann-La Roche Inc., Cranbury, New Jersey 08512). The Arteriosonde was connected to a matching analog recorder (Arteriocorder$^{R}$, same firm). The principles of blood pressure measurement by Doppler ultrasound, employed by this device, have been described in section 1.2.2.4. The power was switched on 30 minutes before operation, permitting warm-up and stabilization of the detector and recorder. Before every measurement session, the Arteriocorder$^{R}$ was calibrated according to the manufacturer's instructions: after inserting the special calibrating scale, the calibrate, systolic and diastolic lines were set to the appropriate levels. The speed of the recorder was preset at 4.5 hours for the entire record. The maximal cuff inflation pressure was set to a point 30 mmHg higher than the auscultatory systolic pressure, using the appropriate front panel adjustment of the Arteriosonde$^{R}$. The deflation rate was set at three heart beats per 10 mmHg. The ultrasound transducer was placed in its holder in the cuff and covered with a water soluble ultrasound transmission gel (Aquasonic$^{R}$, Parker Laboratories Inc., Orange, N.J. 07050, U.S.A.).

The cuff was then applied so that the transducer lay directly over the brachial artery of the right upper arm. The length of the cuff was 42 cm; the size of the air bag 12 x 23 cm.

The same cuff size was employed in all patients. Although it was realised that this practice might lead to a systematic over- or underestimation of the actual blood pressure in very obese or very thin individuals, respectively, the objective of this study was to measure blood pressure changes in the individual subjects. Since the arm circumference of an individual subject remains relatively constant, even in the longitudinal study, the measurement of blood pressure differences should not be affected by the use of the single cuff size.

The front panel of the Arteriosonde$^{R}$ contains two separate mercury columns. Both columns rise to reflect inflation pressure in the cuff, then fall slowly as the cuff pressure is reduced. One moving mercury column stops as soon as the systolic blood pressure is detected, and the other stops when the diastolic blood pressure is found, in such a way that systolic blood pressure corresponds to the pressure at the first Korotkow sound, and diastolic pressure to the pressure at the fifth Korotkow sound of the auscultatory method. Note that Korotkow sounds are not detected by this method (see section 1.4.3).
The first measurements were controlled with a stethoscope. If the cuff was at the appropiate site, the transmission in order and the patient at rest, then the frequency of the automatic blood pressure determinations was set at one recording per five minutes. Measurements were made at intervals of five minutes for one hour. Then the subject was turned to the left lateral position and readings continued for a second hour.

At the very beginning of the study the Arteriosonde$^{R}$ was thoroughly checked, cleaned and the columns filled with new mercury.

Since manipulation and conversation during the position change may also effect the blood pressure (GINSBURG and DUNCAN, 1969; HOVINGA et al., 1978), the influence of these non-specific stimuli was removed by excluding several periods immediately before and

after the position change from the analysis. Figure 7.1.3 shows that the first three and the last readings in each position are left out. Thus nine readings in each position were used for further analyses.

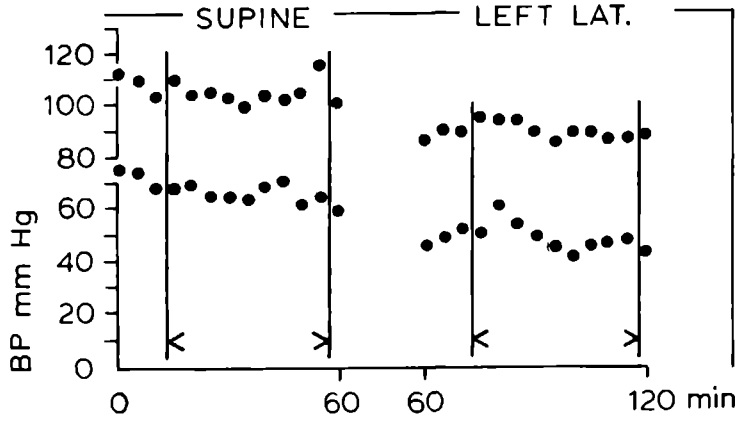



Fig. 7.1.3 Blood pressure recording with the Arteriosonde$^{R}$. Statistical analyses of values between vertical rules only.

The pulse pressure (P) was calculated as the difference between the systolic (S) and diastolic (D) blood pressure.

The mean arterial pressure (M) was calculated as the diastolic blood pressure plus 1/3 pulse pressure.

The differences between the systolic, diastolic, mean arterial and pulse pressures in the supine and left lateral positions were calculated and were called the postural (positional) blood pressure differences ($\Delta S$, $\Delta D$, $\Delta M$, $\Delta P$).

For $\Delta P$ defined as $\Delta(S-D)$ also $\Delta P=\Delta S-\Delta D$ may be written. For the systolic, diastolic and mean arterial blood pressure the average blood pressure of supine and left lateral positions are calculated and denoted as ASBP, ADBP and AMBP, respectively.

### *7.1.4 Delivery data*

After delivery of the infant, the following data were recorded:

- Amenorrhoea at the time of delivery.
- Birth weight of the infant and the birth weight percentile according to the tables of intrauterine growth for the Dutch population (KLOOSTERMAN, 1973).

  Pregnancy outcome in this study is defined in 2 ways: the birth weight percentile of the infant and delivery of an infant which was or was not growth retarded (i.e. birth weight below or above the 10th percentile).
- Weight of the placenta (without membranes and cord).
- Presence or absence of infarcts in the placenta.
- Sex of the infant.
- Perinatal mortality, defined as the death of an infant occurring before, during or after birth within the period from the end of the 27th week of pregnancy to the end of the 7th day of postnatal life (W.H.O., 1965).

### *7.2 Data processing and analyses*

#### *7.2.1 Data processing*

The collected data were coded on special sheets for key-punching. The computer of the U.R.C. (Universitair Reken Centrum, Nijmegen University) was used for data quality control and statistical analyses. The analysis strategies were developed in collaboration with the statistical consultant (M.A. van 't Hof, Department for Statistical Consultation, University of Nijmegen; Head: Ph. van Elteren).

#### *7.2.2 Statistical methods*

An impression of the accuracy of a measurement may be obtained by duplicate measurements. The duplicate measurement error (e) is a measure for the reproducibility and is calculated as $e = \sqrt{\Sigma d_i^2/2n}$ in which $d_i$ = the difference between both measurements of the $i^{th}$ pair, n = the number of paired observations.

In order to test hypotheses several different statistical tests were applied (BAHN, 1972). A p-value $\leq 0.05$ was used as level

of significance. The symbol NS (not significant) includes a p-value >0.05. Depending on the situation the following tests were used:

Student's one-sample t-test was used when the mean value of a series of observations (often differences of two observations in the same individual) had to be tested against zero. The test statistic is the t-value following the Student distribution with n-1 degrees of freedom (n number of observations).

In the case that only dichotomious data are available, such as the pairs yes/no, positive/negative, smaller/larger, the sign test was used, based on the binomial distribution.

When two different groups are involved, Student's two-sample t-test was used in order to test the difference between the level of both groups. The test statistic is the t-value following the Student distribution with n-2 degrees of freedom (n is the total number of observations).

For the comparison of the mean values of more than two groups the one-way analysis of variance was applied. The test uses the F-statistic depending on k-1 and n-k degrees of freedom, respectively, where k is the number of groups and n the total number of observations.

Relationships between variables were studied by correlation coefficients. Product-moment correlation coefficients were calculated in order to judge how strong the relationship was and were tested against zero according to Pearson's correlation test.

A relationship found may be described by a regression line including two regression coefficients, i.e. intercept and slope.

When one dependent variable had to be explained by several independent variables, the multiple regression coefficients were calculated and tested against zero according to an F-statistic. In addition, the standardized regression coefficients ($\beta$-weights) calculated for each independent variable were tested against zero for the judgment of its contribution to the regression.

In n x k contingency tables the dependency of both classifications was tested by means of the $\chi^2$-statistic depending on (n-1) (k-1) degrees of freedom.

## *7.3 Study subjects*

### *7.3.1 Cross-sectional study*

Blood pressure measurements were performed in a prospective study in 42 control subjects and 125 high risk pregnant nulliparous women.

*Group 1. Non-pregnant control subjects (n=42)*

This group consisted of healthy subjects who had never suffered from hypertension or renal disease.
Excluded from the study were individuals who showed overt hypertension (>140/90 mmHg) at first blood pressure measurement, had overt or suspected diabetes mellitus, or did not belong to the Dutch population.

Group 1 is divided in the following subgroups:

*Group 1a* consisted of 17 healthy men in the age range of 20 to 27 years;

*Group 1b* consisted of 25 non-pregnant nulliparous women in the age range of 19 to 34 years.

Seven of the 25 women were patients admitted to the gynaecologic service of the University Hospital for diagnostic laparoscopy (primary infertility). Patients with major endocrine abnormalities and significant systemic illnesses were excluded from the study.
Eight subjects were asked to have the blood pressure measurements performed at a different time under the same conditions as described in section 7.1.3 to assess reproducibility of the postural changes in blood pressure (see section 8.1.3).

*Group 2. Pregnant nulliparous women (n=125)*

The pregnant subjects in this study (age range 18 to 35 years) were admitted to the University Hospital because of some complication of pregnancy, most frequently hypertension, but also premature rupture of membranes, suspected retarded foetal growth without hypertension, etc. (see Table 7.3.1).

In accordance with established departmental policies, patients with hypertension or with growth retardation were treated with a sodium restricted diet (<20 mmol/24 hrs) and bed rest.

TABLE 7.3.1 INDICATIONS FOR HOSPITAL ADMISSION FOR PREGNANT PATIENTS IN THE CROSS-SECTIONAL STUDY

| | Group 2a n=19 No hypertension | Group 2b n=22 Pre-existing hypertension | Group 2c n=84 PIH only | Total n=125 |
|---|---|---|---|---|
| Hypertension only | 0 | 5 | 19 | 24 (19.2%) |
| Toxaemia | 0 | 8 | 29 | 37 (29.6%) |
| Pre-eclampsia | 0 | 2 | 11 | 13 (10.4%) |
| Growth retardation | 6 | 0 | 1 | 7 (5.6%) |
| Hypert.+growth ret. | 0 | 2 | 10 | 12 (9.6%) |
| Toxaemia+growth ret. | 0 | 3 | 10 | 13 (10.4%) |
| Pre-eclampsia+gr.ret. | 0 | 0 | 3 | 3 (2.4%) |
| Proteinuria | 1 | 0 | 0 | 1 (0.8%) |
| Premature rupture of membranes | 1 | 0 | 1 | 2 (1.6%) |
| Renal disease | 5 | 2 | 0 | 7 (5.6%) |
| Threatened premature labour | 1 | 0 | 0 | 1 (0.8%) |
| Other diseases | 5 | 0 | 0 | 5 (4%) |

Excluded from the study were individuals:
- who had a menstrual age of less than 28 weeks;
- with twin pregnancies;
- with diabetes mellitus;
- who were receiving medication other than ferrous fumarate;
- had polyhydramnios;
- or who showed the "supine hypotensive syndrome".

In 10 subjects the sequence of measurements was alternated between supine-left lateral-supine and left lateral-supine-left

lateral. There was no indication that the sequence of postures affected blood pressure differences (see section 8.1.2).

*Group 2* is divided in the following subgroups:

*Group 2a* consisted of 19 normotensive, pregnant nulliparous subjects. The assessment as normotensive was based on the casual blood pressure readings in supine position by the auscultatory method (see section 7.1.3). If the diastolic pressure did not exceed 90 mmHg, the patient was considered to be normotensive for purposes of this study.
Note that this group may not be regarded as a random sample from healthy pregnant women.

*Group 2b* consisted of 22 subjects with pre-existing hypertension. This diagnosis was made as described in section 7.1.1. They demonstrated aggravation of the hypertension and other evidence of super-imposed toxaemia.

*Group 2c* consisted of 84 pregnant nulliparous women with pregnancy induced hypertension (PIH). PIH is defined as a casual diastolic blood pressure >90 mmHg in the supine position any time after 28 weeks of gestation in subjects without pre-existing hypertension (as defined earlier). Most subjects fitted in the subcategory of toxaemia.

### *7.3.2 Longitudinal study*

Twelve volunteers agreed to have blood pressures studied, as described in section 7.1.3, performed serially during pregnancy. Non-pregnant values were obtained six weeks after delivery. In 3 subjects, the initial blood pressure studies were also done prior to pregnancy.
The blood pressure measurements were performed soon after the first antenatal clinic visit and repeated every 4 weeks until the 28th week of pregnancy. After this time the blood pressure recording session was done every week until the delivery. Puerperal recordings were obtained on the fourth post partum day, and

again after 6 weeks.
The weekly measurements were performed on the same day in the week for each individual patient and at the same time of the day.

### *7.3.3 Reproductive performance of the pregnant subjects in the cross-sectional study*

Before proceeding to the results of the blood pressure measurements, the results of the pregnancies in the study group will be summarized. The major features are listed in Table 7.3.3. The criteria for inclusion of subjects in each of the three groups 2a, 2b and 2c have been already described in section 7.3.1.

TABLE 7.3.3 RESULTS OF PREGNANCY IN THE 125 NULLIPAROUS WOMEN STUDIED

| | Group 2a n=19 No hypertension | Group 2b n=22 Pre-existing hypertension | Group 2c n=84 PIH only | Total n=125 |
|---|---|---|---|---|
| Amen.delivery | | | | |
| Mean | 278.1(13.9)days | 276.3(15.7) | 278.2(14.3) | 277.9(14.4) |
| Range | 241 - 305 | 241 - 306 | 227 - 304 | 227 - 306 |
| Proteinuria | 2 | 8 | 18 | 28(22.4%) |
| Small-for-dates | 5 | 2 | 27 | 34(27.2%) |
| Prematurity | 1 | 5 | 12 | 18(14.4%) |
| Small-for-dates and prematurity | 1 | 1 | 6 | 8(6.4%) |
| Perinatal deaths | 1 | 0 | 1 | 2(1.6%) |

No significant differences were found for the listed variables between the three groups.

Two perinatal deaths occurred in the study group. Both were classified as intrauterine foetal deaths. One foetus died presumably as a result of chronic placental insufficiency in association with maternal pregnancy induced hypertension (group 2c); the second foetus died due to placental abruption, but the mother showed no hypertension (group 2a).

## 8.1 Control of measurement methods

### 8.1.1 Mean versus median values

As explained in section 7.1.3 nine blood pressure recordings in each position were used for calculations. To facilitate analyses we had to choose between mean or median blood pressure values.

In a preliminary study, both the mean and median blood pressure values were used to calculate postural blood pressure differences in 75 control subjects and 69 primigravidae. The individual differences between the postural blood pressure differences based on mean and median blood pressures were calculated. The results are given in Table 8.1.1.

TABLE 8.1.1 AGREEMENTS OF POSTURAL BLOOD PRESSURE DIFFERENCES BASED ON MEAN AND MEDIAN BLOOD PRESSURE VALUES

| | | Systolic | | | Diastolic | | |
|---|---|---|---|---|---|---|---|
| | | Mean | SD | t | Mean | SD | t |
| I | Controls n=75 | 0.05 | 2.3 | 0.20 | 0.1 | 1.9 | 0.58 |
| II | Primigravidae n=69 | 0.29 | 2.3 | 1.05 | -0.08 | 2.0 | 0.33 |

Listed are the means, standard deviations (SD), and t-values (Student's one-sample t-test) for the value ($\Delta$med - $\Delta$mean), where $\Delta$med is the postural blood pressure difference based on the median blood pressures, and $\Delta$mean is the postural blood pressure difference, calculated from the mean blood pressures.

One-sample Student's t-test was used to evaluate possible systematical differences. No difference was found between the mean or median values in either group. Since the mean values in general are more accurate than the median values, the mean values were used for further analyses.

TABLE 8.1.2 POSTURAL BLOOD PRESSURE DIFFERENCES BETWEEN SUBJECTS WITH SEQUENCE OF POSTURES SUPINE - LEFT LATERAL - SUPINE (GROUP A ; n=5) AND LEFT LATERAL - SUPINE - LEFT LATERAL (GROUP B ; n=5)

| | $\Delta 1 = \Delta(S \rightarrow L)$ | $\Delta 2 = \Delta(L \rightarrow S)$ | $\Delta 1 - \Delta 2$ | t-value* | Signi-ficance |
|---|---|---|---|---|---|
| A Systolic | 14.0(3.0) | 13.9(3.9) | 0.1(6.1) | 0.03 | NS |
| B Systolic | 23.8(2.6) | 18.4(7.1) | 5.4(7.7) | 1.40 | NS |
| A + B Syst. | 18.9(5.8) | 16.1(5.9) | 2.8(7.3) | 1.15 | NS |
| A Diastolic | 20.0(4.1) | 13.0(1.7) | 7.0(5.4) | 2.60 | NS |
| B Diastolic | 19.0(8.5) | 19.7(6.6) | 0.7(12.8) | 0.11 | NS |
| A + B Diast. | 19.5(6.3) | 16.3(5.7) | 3.2(10.1) | 0.95 | NS |

Presented are the mean values and standard deviations in parentheses

$\Delta 1$ = postural difference in systolic or diastolic blood pressure with supine as starting position

$\Delta 2$ = postural difference in systolic or diastolic blood pressure with left lateral as starting position

$\Delta 1 - \Delta 2$ = difference of the postural differences

* : t-value according to Student's one-sample t-test for $\Delta 1 - \Delta 2 = 0$ t-value depends on 4 degrees of freedom for groups A or B and on 9 degrees of freedom for A + B

### *8.1.2 Sequence of postures*

In 10 patients the sequence of measurements was alternated between supine-left lateral-supine (group A, 5 patients) and left lateral-supine-left lateral (group B, 5 patients). Groups A and B consisted of subjects from group 2 (pregnant patients).

The postural blood pressure differences were essentially the same in the two groups, regardless of the sequences of postures. Table 8.1.2 shows the results of the one-sample Student's t-test applied to the difference of the difference ($\Delta 1 - \Delta 2$) for systolic, diastolic and mean arterial blood pressures within both groups. The difference of the differences for systolic and diastolic blood pressure, respectively, between groups A and B was analysed using the two-sample Student's t-test. The resulting values ($t=1.20$ and $t=1.01$, respectively) were not significant. Therefore, also the differences ($\Delta 1 - \Delta 2$) were tested in the total group A+B. No significant differences were found.
Thus, there was no indication that the sequence of posture affected blood pressure differences.

Subsequent results obtained by the sequence: supine, then left lateral, as taken in this study, may be generalized to the sequence left lateral-supine.

### *8.1.3 Effective measurement errors: duplicate errors in postural blood pressure differences*

Resting blood pressures were recorded in eight non-pregnant nulliparous control subjects and repeated after two months under the same conditions, as described in section 7.1.3.
The postural differences in systolic, diastolic, mean arterial and pulse pressures in each occasion were calculated. The differences in each value between the two occasions in the individual subject were used to calculate the measurement error (see section 7.2).

The duplicate errors for the positional blood pressure differences were:

- for the systolic value, the measurement error in $\Delta S$=5.5 mmHg;
- for the diastolic value, the measurement error in $\Delta D$=5.5 mmHg;
- for the MAP-value, the measurement error in $\Delta MAP$=4.8 mmHg;
- for the pulse pressure value, the measurement error in $\Delta P$=4.8 mmHg.

It is notable that the error in $\Delta P$ is not larger than in $\Delta S$ or $\Delta D$. The explanation of the reduction in the error of $\Delta P$ is that the errors in $\Delta S$ and $\Delta D$ are positively correlated.

## *8.2 Postural blood pressure differences*

### *8.2.1 Basal blood pressure versus postural blood pressure differences*

The correlation coefficients between the blood pressure in supine position and the postural difference in blood pressure are given in Table 8.2.1.A. This table shows that most of the correlation coefficients and all the significant ones are positive. This suggests that hypertension is related to a greater postural blood pressure difference.

Since the left lateral blood pressure is highly correlated with the blood pressure in the supine position we would expect to see the same tendency for the left lateral blood pressure values. Table 8.2.1.B., however, shows that this is not true. On the contrary, the correlation coefficients in this position are mainly significantly negative. The explanation for this paradox is found in the relatively large measurement error. A high value in the supine position may be partly due to a large positive measurement error. The error in the left lateral position is more or less independent of the error in supine position. Therefore, a large measured postural difference is found in the case that the supine value is overestimated (introducing a positive correlation) or underestimated in the left lateral position

TABLE 8.2.1.A CORRELATION COEFFICIENTS (PEARSON) BETWEEN THE BLOOD PRESSURE AND POSTURAL BLOOD PRESSURE DIFFERENCE IN THE *SUPINE* POSITION

| Groups | n | SBP vs Δ S | DBP vs Δ D |
|---|---|---|---|
| 1a Controls, men | 17 | 0.42* | 0.33 |
| 1b Controls, nulliparae | 25 | 0.22 | 0.22 |
| 2a Pregnant women, no hypertension | 19 | -0.09 | 0.15 |
| 2b Pregnant women, pre-existing hypertension | 22 | 0.49* | 0.10 |
| 2c Pregnant women, pregnancy induced hypertension | 84 | 0.22* | 0.22* |

TABLE 8.2.1.B CORRELATION COEFFICIENTS (PEARSON) BETWEEN THE BLOOD PRESSURE AND POSTURAL BLOOD PRESSURE DIFFERENCE IN THE *LEFT LATERAL* POSITION

| Groups | n | SBP vs Δ S | DBP vs Δ D |
|---|---|---|---|
| 1a Controls, men | 17 | -0.17 | -0.39 |
| 1b Controls, nulliparae | 25 | -0.23 | -0.24 |
| 2a Pregnant women, no hypertension | 19 | -0.48* | -0.57** |
| 2b Pregnant women, pre-existing hypertension | 22 | -0.09 | -0.48* |
| 2c Pregnant women, pregnancy induced hypertension | 84 | -0.31** | -0.33** |

SBP, systolic blood pressure; DBP, diastolic blood pressure; Δ , postural blood pressure difference.

* : $p<0.05$

** : $p<0.01$

(introducing a negative correlation). In such a situation the average blood pressure of both positions will not demonstrate any correlation with the postural differences, which is confirmed by the correlation coefficients shown in Table 8.2.1.C.

TABLE 8.2.1.C CORRELATION COEFFICIENTS (PEARSON) BETWEEN THE *AVERAGE* BLOOD PRESSURE AND POSTURAL BLOOD PRESSURE DIFFERENCE

| Groups | | n | ASBP vs Δ S | ADBP vs Δ D |
|---|---|---|---|---|
| 1a | Controls, men | 17 | 0.14 | -0.03 |
| 1a | Controls, nulliparae | 25 | -0.01 | -0.01 |
| 2a | Pregnant women, no hypertension | 19 | -0.30 | -0.26 |
| 2b | Pregnant women, pre-existing hypertension | 22 | 0.23 | -0.22 |
| 2c | Pregnant women, pregnancy induced hypertension | 84 | -0.05 | -0.06 |

Average blood pressure : $\frac{\text{supine BP + left lateral BP}}{2}$ mmHg ;

ASBP, average systolic blood pressure; ADBP, average diastolic blood pressure; Δ, postural blood pressure difference

There is no correlation between the "true" basal blood pressure and the "true" postural difference in blood pressure. Thus, the significant correlations in Tables 8.2.1.A and 8.2.1.B are due to measurement error. This phenomenon is called the phenomenon of correlation with initial value (in this case the supine value) or more in general "regression to the mean" (VAN 'T HOF, 1977).

*Main point*

Differences in blood pressure between supine and left lateral positions were unrelated to basal blood pressures.

### *8.2.2 Postural blood pressure differences in non-pregnant and pregnant normotensive subjects*

In 17 non-pregnant nulliparous control subjects, 9 were taking

TABLE 8.2.2.A BLOOD PRESSURES AND POSTURAL BLOOD PRESSURE DIFFERENCES IN 17 NON-PREGNANT NULLIPAROUS CONTROL SUBJECTS IN DIFFERENT STAGES OF THE CYCLE

| | | Pre-ovulatory phase n=4 | Post-ovulatory phase n=4 | "Pill" n=9 | Signi-ficance * |
|---|---|---|---|---|---|
| Supine | | | | | |
| | S | 132.2(14.3) | 115.7(9.3) | 120.2(8.0) | NS |
| | D | 82.0(9.8) | 69.7(8.9) | 70.7(11.0) | NS |
| | M | 115.5(12.9) | 100.2(8.6) | 103.9(7.2) | NS |
| | P | 50.2(5.6) | 46.0(8.2) | 49.5(11.5) | NS |
| Left lateral | S | 121.0(9.8) | 105.7(11.1) | 108.7(7.7) | NS |
| | D | 68.7(7.1) | 57.5(9.7) | 57.4(9.5) | NS |
| | M | 103.7(8.6) | 89.5(10.4) | 91.4(8.1) | NS |
| | P | 52.3(9.5) | 48.2(5.4) | 51.3(6.3) | NS |
| | Δ S | 11.2(5.4) | 10.0(4.0) | 11.5(4.8) | NS |
| | Δ D | 13.3(3.9) | 12.2(3.9) | 13.3(5.7) | NS |
| | Δ M | 11.8(4.3) | 10.7(3.1) | 12.5(4.1) | NS |
| | Δ P | -2.1(4.8) | -2.2(4.0) | -1.8(6.6) | NS |

Presented are the mean values and standard deviations in parentheses

S, systolic; D, diastolic; M, mean arterial pressure; P, pulse pressure; Δ, postural difference

All values in mmHg

* : One-way analysis of variance

the "pill", 4 were in the pre-ovulatory phase and another 4 in the post-ovulatory stage of the cycle. No significant differences in blood pressures and postural blood pressure differences between the three groups were found (see Table 8.2.2.A).

Therefore, in further analyses the non-pregnant female subjects were considered as one control group.

The mean supine, left lateral and average blood pressure values and the postural differences in blood pressure for male and female control subjects and normotensive pregnant nulliparae are given in Table 8.2.2.B.

Since the postural differences in blood pressure between the heart and site of blood pressure measurement are at least partly due to positional hydrostatic pressure differences, we measured the distance between the xiphoid process and the right arm, i.e. the approximate distance from the right atrium to the right brachial artery, in the 17 male control subjects and in 17 of the 25 nulliparous female controls. The distance from the right atrium to the right brachial artery was greater in the men than in the nulliparous women (15.5 and 13.9 cm, respectively, Student's t-test, $p<0.05$ ; Table 8.2.2.B).
The hydrostatic pressure contribution to the postural blood pressure differences can be estimated from these right arm - xiphoid distances. If the specific gravity of blood plasma is taken to be 1.030 (BARD, 1956), the mean hydrostatic pressure component can be calculated to be 11.7 mmHg for the men and 10.5 mmHg for the women. The observed mean postural blood pressure differences were 1 to 3 mmHg greater than these calculated values (Table 8.2.2.B).

The mean postural differences for systolic, diastolic, mean arterial blood pressures and pulse pressures for the normotensive pregnant patients were not significantly different from that observed in the non-pregnant control groups (One-way analysis of variance ; $p>0.1$; Table 8.2.2.B).
For all the three groups the postural differences in pulse pressure ($\Delta P$) were not significantly different from zero (Table 8.2.2.B).

TABLE 8.2.2.B BLOOD PRESSURES AND POSTURAL BLOOD PRESSURE DIFFERENCES IN NON-PREGNANT AND PREGNANT NORMOTENSIVE SUBJECTS

| | | Group 1a Men n=17 | Group 1b Non-pregnant nulliparae n=25 | Group 2a Pregnant normotensive nulliparae n=19 | Significance** |
|---|---|---|---|---|---|
| Atrium-brachial artery distance (cm) | | 15.5(1.6) | 13.9(1.9)* | - | p<0.05 |
| Supine | S | 124.5(13.3) | 122.3(10.6) | 120.9(9.4) | NS |
| | D | 75.6(9.0) | 74.2(9.8) | 75.5(7.5) | NS |
| | M | 108.2(11.0) | 106.3(9.6) | 105.6(7.4) | NS |
| | P | 49.2(10.1) | 48.1(8.1) | 45.4(10.5) | NS |
| Left lateral | S | 111.8(12.3) | 110.0(10.7) | 106.9(10.7) | NS |
| | D | 61.0(9.2) | 61.8(9.8) | 59.6(9.1) | NS |
| | M | 95.1(10.5) | 94.5(10.1) | 91.2(8.5) | NS |
| | P | 50.8(9.5) | 49.2(6.3) | 47.3(12.1) | NS |
| Average BP | S | 118.3(12.2) | 116.6(10.4) | 113.9(9.9) | NS |
| | D | 68.3(8.4) | 68.0(9.5) | 67.6(7.8) | NS |
| | M | 101.6(10.3) | 100.4(9.6) | 98.4(7.7) | NS |
| | P | 50.0(8.6) | 48.6(6.7) | 46.3(11.0) | NS |
| | Δ S | 13.1(7.7) | 11.3(4.9) | 14.0(4.3) | NS |
| | Δ D | 14.6(6.6) | 12.4(4.5) | 15.9(6.3) | NS |
| | Δ M | 13.2(6.0) | 11.8(3.9) | 14.4(4.0) | NS |
| | Δ P | -1.5(9.3) | -1.1(5.3) | -1.9(5.8) | NS |
| p-value *** | | p>0.1 | p>0.1 | p>0.1 | |

Presented are the mean values and standard deviations in parentheses

S, systolic; D, diastolic; M, mean arterial pressure, P, pulse pressure; Δ, postural difference

All values in mmHg.

* : n=17

** : One-way analysis of variance or two-sample Student's test

*** : One-sample Student's t-test for testing the significance of ΔS-ΔD(ΔP) against 0

*Main points*

In the non-pregnant subjects the mean postural differences in blood pressure between supine and left lateral positions approximated the values expected from the hydrostatic pressure gradient.

Normotensive pregnancy did not significantly affect the postural blood pressure differences. The postural differences in diastolic blood pressure (ΔD) were not significantly greater than the postural difference in systolic blood pressures (ΔS).

### *8.2.3 Postural blood pressure differences in normotensive and hypertensive gravidae*

The data for the pregnant patients in Table 8.2.3.A are presented in three groups according to whether the gravida was normotensive (2a), had hypertension predating pregnancy (2b) or had become hypertensive during pregnancy (2c).

The mean age, the duration of amenorrhoea at the time of study and at the time of delivery, and the reproductive performance are presented in Tables 7.3.3 and 8.2.3.B. The variables listed did not show significant differences between the three groups (2a, 2b, 2c). Therefore, the groups offer good opportunities to analyse differences in blood pressure parameters.

TABLE 8.2.3.B AGE AND AMENORRHOEA AT THE TIME OF BLOOD PRESSURE MEASUREMENT IN NORMOTENSIVE AND HYPERTENSIVE GRAVIDAE

| | | Group 2a n=19 No hypertension | Group 2b n=22 Pre-existing hypertension | Group 2c n=84 PIH only | Significance* |
|---|---|---|---|---|---|
| Age (years) | Mean | 25.0(3.6) | 26.7(3.7) | 26.4(3.7) | NS |
| | Range | 19 - 33 | 21 - 34 | 18 - 34 | |
| Amen.at study (days) | Mean | 252.8(25.2) | 261.7(20.4) | 262.1(21.6) | NS |
| | Range | 203 - 302 | 219 - 289 | 196 - 301 | |

The standard deviations are presented in parentheses

* : One-way analysis of variance

TABLE 8.2.3.A BLOOD PRESSURES AND POSTURAL BLOOD PRESSURE DIFFERENCES IN NORMOTENSIVE AND HYPERTENSIVE GRAVIDAE

| | | Group 2a n=19 No hypertension | Group 2b n=22 Pre-existing hypertension | Group c n=84 P.I.H. only | Signifi-cance* |
|---|---|---|---|---|---|
| Supine | S | 120.9(9.4) | 129.8(11.8) | 129.6(11.6) | p<0.05 |
| | D | 75.5(7.5) | 91.9(9.0) | 86.9(9.8) | p<0.01 |
| | M | 105.6(7.4) | 117.0(10.3) | 115.3(10.2) | p<0.01 |
| | P | 45.4(10.5) | 37.9(8.3) | 42.7(8.7) | p<0.05 |
| Left lateral | S | 106.9(10.7) | 117.9(10.3) | 117.0(12.0) | p<0.01 |
| | D | 59.6(9.1) | 73.2(10.2) | 69.3(10.1) | p<0.01 |
| | M | 91.2(8.5) | 103.0(9.5) | 101.1(10.3) | p<0.01 |
| | P | 47.3(12.1) | 44.7(8.1) | 47.8(10.2) | NS |
| Average BP | S | 113.9(9.9) | 123.8(10.6) | 123.3(11.4) | p<0.01 |
| | D | 67.6(7.8) | 82.6(9.2) | 78.1(9.6) | p<0.01 |
| | M | 98.4(7.7) | 109.9(9.5) | 108.2(9.9) | p<0.01 |
| | P | 46.3(11.0) | 41.2(7.6) | 45.2(8.9) | NS |
| | Δ S | 14.0(4.3) | 11.9(6.8) | 12.5(6.2) | NS |
| | Δ D | 15.9(6.3) | 18.6(5.7) | 17.6(5.5) | NS |
| | Δ M | 14.4(4.0) | 14.0(6.0) | 14.1(5.1) | NS |
| | Δ P | -1.9(5.8) | -6.7(6.1) | -5.1(6.6) | p=0.05 |
| p - values ** | | p>0.1 | p<0.01 | p<0.01 | |

Presented are the mean values and standard deviations in parentheses

S, systolic; D, diastolic; M, mean arterial pressure; P, pulse pressure; Δ, postural difference

All values in mmHg.

* : p-values for the one-way analyses of variance for the differences between the three groups

** : One-sample Student's t-test ; p-value for testing the significance ΔS-ΔD (ΔP) against 0

The mean systolic, diastolic and mean arterial *blood pressures* in both supine and left lateral positions in the pre-existing hypertensive and PIH-groups were, as expected, significantly greater (One-way analysis of variance) than the corresponding values in the normotensive group (see Table 8.2.3.A). The blood pressures of the gravidae with pre-existing or pregnancy induced hypertension (PIH) were also significantly higher than those of the control group (One-way analysis of variance).

The pulse pressures in the supine position in both hypertensive groups were lower than in the normotensive gravidae, while in the left lateral position no differences were found in pulse pressure between hypertensive and normotensive gravidae (One-way analysis of variance).

The *postural differences* in systolic, diastolic and mean arterial blood pressures did not differ significantly between the three subgroups of pregnant subjects (One-way analysis of variance). However, in both of the hypertensive groups the postural differences in diastolic blood pressures were significantly greater than the corresponding postural difference in systolic blood pressure, since both hypertensive groups (2b, 2c) showed significant negative mean values for the postural differences in pulse pressure ($\Delta P$, see Table 8.2.3.A). This was not demonstrated in the normotensive gravidae. Additionally, the $\Delta P$'s were significantly lower in the two hypertensive groups (2b, 2c) than in the normotensive group (One-way analysis of variance, $p=0.05$).

*Main points*

Postural differences in systolic, diastolic and mean arterial blood pressures did not differ significantly between normotensive gravidae and gravidae with pre-existing or pregnancy induced hypertension.

In both hypertensive groups (2b, 2c) the postural differences in diastolic blood pressure were significantly greater than the corresponding values of the systolic parameter (i.e. $\Delta P < 0$).

The postural differences in pulse pressure (ΔP) in the hypertensive groups are significantly smaller than the ΔP in the normotensive group. This is due to smaller pulse pressures in the supine position in the hypertensive groups than in the normotensive group, while the pulse pressures in the left lateral position are equal among the three pregnant groups.

### *8.2.4 Blood pressure, postural blood pressure differences and pregnancy outcome*

In the group of women who developed pregnancy induced hypertension (2c), statistically significant correlations were observed between 5 of the 8 maternal *baseline blood pressure parameters* and infant birth weight percentile (Table 8.2.4.A).
Similar conclusions may be drawn from Table 8.2.4.B. It is shown that the baseline blood pressure parameters in the supine position were significantly higher in those women with PIH who later gave birth to growth retarded infants than in the gravidae with normally - grown infants. The same trend was present for the left lateral blood pressure values, but the difference was statistically significant only for the mean arterial blood pressure (MAP).

Both other groups show the same tendency but not a significant level, probably due to smaller sample size (Tables 8.2.4.A and B).

There were in the group of patients with PIH (2c) significant correlations between the infant birth weight percentile and the *postural differences* in systolic and mean arterial blood pressures (Table 8.2.4.A). No significant correlations were found between birth weight percentile and postural differences in diastolic blood pressure and pulse pressure. When the PIH-patients were divided on the basis of infant weight above or below the 10th percentile, however, this phenomenon disappeared (Table 8.2.4.B).

Because, in the PIH-group, statistically significant correlations were demonstrated between both baseline and postural

TABLE 8.2.4.A CORRELATION COEFFICIENTS (PEARSON) BETWEEN BIRTH WEIGHT PERCENTILES AND BLOOD PRESSURE PARAMETERS IN NORMOTENSIVE AND HYPERTENSIVE GRAVIDAE

| | | Group 2a n=19 No hypertension | Group 2b n=22 Pre-existing hypertension | Group 2c n=84 P.I.H. only |
|---|---|---|---|---|
| Supine | S | -0.18 | -0.19 | -0.30* |
| | D | -0.12 | -0.29 | -0.31* |
| | M | -0.19 | -0.24 | -0.33* |
| | P | -0.08 | -0.05 | -0.05 |
| Left lateral | S | -0.17 | -0.16 | -0.16 |
| | D | -0.21 | -0.34 | -0.25* |
| | M | -0.22 | -0.24 | -0.21* |
| | P | 0.00 | 0.22 | -0.05 |
| | Δ S | 0.03 | -0.08 | -0.24* |
| | Δ D | 0.15 | 0.14 | -0.10 |
| | Δ M | 0.12 | -0.03 | -0.23* |
| | Δ P | -0.15 | -0.22 | -0.14 |

TABLE 8.2.4.C MULTIPLE REGRESSION ANALYSIS OF THE AVERAGE BLOOD PRESSURE AND POSTURAL BLOOD PRESSURE DIFFERENCE ON THE BIRTH WEIGHT PERCENTILE

| | | Group 2a n=19 No hypertension | Group 2b n=22 Pre-existing hypertension | Group 2c n=84 P.I.H. only |
|---|---|---|---|---|
| ASBP | R | 0.14 | 0.17 | 0.35* |
| | $F_{BP}$ | 0.3 | 0.5 | 6.2* |
| | $F_{\Delta}$ | 0.0 | 0.0 | 6.3* |
| ADBP | R | 0.28 | 0.33 | 0.31* |
| | $F_{BP}$ | 0.1 | 0.0 | 8.0* |
| | $F_{\Delta}$ | 0.9 | 0.1 | 1.4 |
| AMBP | R | 0.20 | 0.23 | 0.36* |
| | $F_{BP}$ | 0.4 | 1.1 | 7.5* |
| | $F_{\Delta}$ | 0.1 | 0.0 | 5.1* |

S, systolic; D, diastolic; M, mean arterial pressure, P, pulse pressure; Δ, postural difference; ASBP, average systolic blood pressure; ADBP, average diastolic blood pressure; AMBP, average mean arterial blood pressure

* : $p<0.05$

R , multiple regression coefficient;
$F_{BP}$ , F-ratio for the influence of the average blood pressure (see section 7.1.3);
$F_{\Delta}$ , F-ratio for the influence of postural blood pressure change.

TABLE 8.2.4.B BLOOD PRESSURES AND POSTURAL BLOOD PRESSURE DIFFERENCES IN GROUPS WITH BIRTH WEIGHT PERCENTILES ABOVE OR BELOW THE 10TH PERCENTILE IN NORMOTENSIVE AND HYPERTENSIVE GRAVIDAE

| | | Group 2a n=19 No hypertension | | Group 2b n=22 Pre-existing hypertension | | Group 2c n=84 P.I.H. only | |
|---|---|---|---|---|---|---|---|
| | | ⩾10th %ile n=14 | <10th %ile n=5 | ⩾10th %ile n=20 | <10th %ile n=2 | ⩾10th %ile n=57 | <10th %ile n=27 |
| Supine | S | 121.6(10.8) | 119.0(4.2) | 128.6(11.5) | 141.5(12.0) | 127.1(11.2) | 134.7(11.0)** |
| | D | 75.8(8.6) | 74.8(4.3) | 90.9(8.8) | 102.0(4.2) | 85.3(9.5) | 90.3(9.6)* |
| | M | 106.2(8.3) | 104.0(3.7) | 115.8(9.9) | 128.5(9.2) | 113.1(9.7) | 119.9(9.8)** |
| | P | 45.8(12.2) | 44.2(2.8) | 37.8(8.5) | 39.5(7.8) | 41.8(9.1) | 44.4(7.7) |
| Left lateral | S | 107.4(12.0) | 105.4(6.9) | 116.5(9.5) | 131.5(10.6)* | 115.4(11.8) | 120.4(11.8) |
| | D | 59.9(9.7) | 58.8(8.1) | 72.4(10.3) | 81.5(2.1) | 67.8(10.1) | 72.4(9.5) |
| | M | 91.6(9.4) | 90.0(6.0) | 101.8(9.0) | 114.5(7.8) | 99.6(10.1) | 104.5(10.1)* |
| | P | 47.5(13.5) | 46.6(8.3) | 44.1(8.1) | 50.5(8.5) | 47.6(10.6) | 48.1(9.3) |
| Δ | S | 14.1(4.5) | 13.6(4.3) | 12.1(7.1) | 10.0(1.4) | 11.7(5.6) | 14.3(7.0) |
| Δ | D | 15.8(5.9) | 16.0(8.0) | 18.5(6.0) | 20.5(2.1) | 17.5(5.6) | 18.0(5.4) |
| Δ | M | 14.5(3.9) | 14.0(4.5) | 14.0(6.3) | 14.0(1.4) | 13.6(4.8) | 15.4(5.6) |
| Δ | P | -1.7(5.8) | -2.4(6.3) | -6.4(6.3) | -10.5(0.7) | -5.8(6.5) | -3.7(6.9) |

Presented are the mean values and the standard deviations in parentheses

S, systolic; D, diastolic; M, mean arterial pressure; P, pulse pressure; Δ, postural difference

All values in mmHg

Two-sample Student's test * : $p<0.05$
** : $p<0.01$

difference parameters and birth weight percentile, a multiple regression analysis was performed in order to establish how the combinations of both factors (baseline and postural blood pressures) are useful to explain the differences in birth weight percentile.
The average of the blood pressure values in supine and left lateral positions (ASBP, ADBP and AMBP, see section 7.1.3) was used as baseline blood pressure value in this analysis, since the average blood pressure is less influenced by measurement error than either the supine or left lateral blood pressure values alone, while it has been shown that the average blood pressure is not correlated with the postural blood pressure change (Table 8.2.1.C).
The results of this multiple regression analysis are presented in Tabel 8.2.4.C. Significant ($p<0.05$)multiple correlations were found only in the PIH-group (2c), as could be expected. Here, the multiple regression coefficients were significant for the average systolic, diastolic and mean arterial blood pressures.
Inspection of the F-values, which indicate the relative contribution of the individual factors to the multiple regression, indicates that in the case of systolic and mean arterial blood pressures the baseline pressure and the positional change were both of importance.
In the case of the diastolic parameters, the effect of baseline blood pressure was by far the stronger, and the contribution of positional change was insignificant.

*Main points*

In gravidae with pregnancy induced hypertension statistically significant negative correlations were observed between 5 of the 8 baseline maternal blood parameters and infant birth weight percentile.
Four of the 8 baseline blood pressure parameters of women giving birth to dysmature infants were significantly higher than those of women delivering infants with weights above the 10th

percentile. These relationships were not significant in the other two groups (2a, 2b), although the same tendency is shown.

The postural changes in systolic and mean arterial blood pressures were significantly correlated with infant birth weight percentile, but not with dysmaturity.

In the PIH-group (2c) multiple regression analysis indicated significant relationships between infant birth weight percentile and the following maternal blood pressure parameters: average systolic blood pressure (ASBP), average diastolic blood pressure (ADBP), average mean arterial blood pressure (AMBP), postural differences in systolic ($\Delta$S) and diastolic blood pressure ($\Delta$D).

The postural differences in diastolic ($\Delta$D) and pulse pressure ($\Delta$P) were correlated with neither infant birth weight percentile nor dysmaturity.

### *8.2.5 Influence of proteinuria on blood pressure, postural blood pressure differences and pregnancy outcome*

Significant correlations between the absolute blood pressure parameters and the occurrence of growth retardation were found only in the group of women who developed pregnancy induced hypertension (group 2c; Table 8.2.4.B). This was, however, the largest group and also contained the majority (18) of the 28 patients with proteinuria (Table 7.3.3.). Therefore, this group was analysed for possible relationships between proteinuria and blood pressure parameters and between proteinuria and birth weight percentiles.

The patients in the PIH-group (2c) were divided according to the presence or absence of proteinuria. Blood pressure variables and pregnancy outcome were compared between the two subgroups thus created (Tables 8.2.5.A and 8.2.5.B). Inspection of these tables reveals that no significant differences were found in any of the resting blood pressure parameters or postural differences, or in the incidence of subsequent birth of a

TABLE 8.2.5.A BLOOD PRESSURES AND POSTURAL BLOOD PRESSURE DIFFERENCES ACCORDING TO PRESENCE OR ABSENCE OF PROTEINURIA IN GRAVIDAE WITH PREGNANCY INDUCED HYPERTENSION (Group 2c)

| | | No proteinuria n=66 | Proteinuria n=18 | Significance* |
|---|---|---|---|---|
| Supine | S | 129.3(10.6) | 130.6(14.9) | NS |
| | D | 86.5(9.0) | 88.4(12.5) | NS |
| | M | 115.0(9.2) | 116.5(13.5) | NS |
| | P | 42.8(8.9) | 42.2(8.4) | NS |
| Left lateral | S | 117.1(11.0) | 116.8(15.3) | NS |
| | D | 68.7(9.8) | 71.5(11.2) | NS |
| | M | 101.0(9.5) | 101.7(13.2) | NS |
| | P | 48.4(10.0) | 45.3(10.8) | NS |
| | Δ S | 12.2(6.4) | 13.8(5.2) | NS |
| | Δ D | 17.8(5.5) | 16.9(5.6) | NS |
| | Δ M | 14.0(5.4) | 14.9(3.8) | NS |
| | Δ P | -5.6(6.2) | -3.1(8.0) | NS |

Presented are the mean values and the standard deviations in parentheses

S, systolic; D, diastolic; M, mean arterial pressure; P, pulse pressure; Δ, postural difference.

All values in mmHg.

* Student's test

TABLE 8.2.5.B PROTEINURIA AND THE OUTCOME OF PREGNANCY, EXPRESSED IN BIRTH WEIGHT ABOVE OR BELOW THE 10TH PERCENTILE, IN GRAVIDAE WITH PREGNANCY INDUCED HYPERTENSION (Group 2c)

| | ⩾10th %ile | <10th %ile | Totals |
|---|---|---|---|
| No proteinuria | 48 | 18 | 66 |
| Proteinuria | 9 | 9 | 18 |
| Totals | 57 | 27 | 84 |

$\chi^2_{1df} = 2.39$ (NS)

dysmature infant, according to the presence or absence of proteinuria.

*Main point*

In the patients with pregnancy induced hypertension, the presence or absence of proteinuria did not affect the blood pressure parameters nor the incidence of dysmaturity.

## *8.3 Discussion and conclusions*

The pregnant subjects in this study were not a randomly selected sample representing a normal pregnant population. All patients in the cross-sectional study were admitted to the hospital because of actual or suspected complications of pregnancy (see Table 7.3.1). This make-up of the study group must be kept in mind when interpreting the blood pressure values and pregnancy outcomes.
On the other hand, the objective of the study was to investigate whether or not a relationship exists between postural differences in blood pressure and growth retardation. It might be expected that, should such a relationship exist, it would be most evident in a population such as the one selected for this study: i.e. one including a large proportion of gravidae with one or another hypertensive disorder and thus at high risk for delivery of a dysmature infant. This latter expectation, a high percentage of low birth weight infants, was indeed realized. The number of dysmature infants in the cross-sectional study, 34, was nearly three times that to be expected in a randomly selected population.

Nonetheless, the possibility exists that many of the results described herein, and especially the relationship between blood pressure variables and pregnancy outcome, were strongly influenced by the selection of the study population. The conclusions of this study, therefore, should not be extended to a normal obstetric population, or indeed to gravidae with other pregnancy complications, without prior verification in an appropriate study group.

The blood pressures in the subjects studied were taken in the right upper-arm under standardized conditions in respect to posture, i.e. in both supine and left lateral positions (see section 7.1.3).

In the left lateral position the heart is lower than the site of blood pressure measurement, whereas in the supine position the heart and the site of the blood pressure measurement lie in about the same horizontal plane. Thus the measured blood pressure values in the left lateral position will be lower than in the supine position due to the hydrostatic pressure differences, because in left lateral recumbency the right arm is above heart level. Figure 7.1.3 shows such a difference in an ultrasound recording in the two positions.

It was already pointed out in section 8.2.2 that the measured distance from the xiphoid process to the right-upper arm, converted to a mean hydrostatic component, approximated the postural difference in systolic and diastolic blood pressure (Table 8.2.2.B) in both non-pregnant control subjects and normotensive pregnant patients. However, the observed postural blood pressure differences were 1 to 3 mmHg greater than these calculated values (Table 8.2.2.B). This small remaining difference may be partly explained by the fact that the arm-xiphoid distance was measured from the medial surface of the arm, whereas the brachial artery actually lies 1 to 2 cm further away, deep along the humerus. In addition, the heart shifts slightly towards the side on which the subject is lying (see section 4.2.1) and thus, in left lateral recumbency the right brachial artery-to-heart distance is further increased in this position.

The normotensive gravidae showed slightly (but not significantly) higher postural blood pressure differences than the non-pregnant control subjects. This can partly be explained because during pregnancy the rib margins are elevated and flared, thus increasing the transverse diameter of the chest (HYTTEN and LEITCH, 1971). Also, the diaphragm is elevated and the heart assumes a more transverse position (COOLEY and SCHREIBER, 1968). These anatomic changes tend to increase the physical distance

and thus the hydrostatic pressure gradient between right arm and heart in the left lateral position in pregnant subjects.

In sections 4.2.1 and 4.2.2, the work of various authors was cited, showing that in both non-pregnant and pregnant subjects, the hydrostatic pressure difference played an important role in determining the blood pressure measured in the two different positions.

STEIN (1952) and SCHREIBER (1954) showed in male patients the phenomenon of the higher supine blood pressure as compared to that in the left lateral position. However, shifting and rotation of the heart was thought to be of more importance than the hydrostatic pressure difference.

The results of three studies in non-pregnant women, taken together, further demonstrate the importance of hydrostatic pressure and site of measurement in determining postural blood pressure differences. TROWER and WALTERS (1968) measured postural blood pressure differences (supine versus left lateral) by the auscultatory method, and found an average difference of approximately 15 mmHg. LEES et al. (1967) and LUCAS et al. (1979), using direct intra-arterial measurements, found no postural change. In the study of LEES et al. (1967), the strain gauge in both positions was set at "heart level", while LUCAS et al. (1979), used a catheter-tip strain gauge within the ascending aorta. Thus, in these latter studies, the effect of hydrostatic pressure was eliminated and, with it, the difference in blood pressure between the two positions.

Normotensive pregnant patients showed the same pattern: postural differences were found when indirect methods were used (ESKES et al., 1974; SCANLON, 1974), whereas no or minimal postural blood pressure changes were observed when an intra-aortic strain gauge was employed (LUCAS et al., 1979), or when an external strain gauge was set at heart level (LEES et al., 1967).

Not all investigators have obtained similar results : GINSBURG and DUNCAN (1969) and HOVINGA et al. (1978), both groups using intra-arterial catheters with external strain gauges, found differences in blood pressure between supine and a lateral position. In the study of GINSBURG and DUNCAN (1969), the blood pressure averaged

higher in the lateral position, whereas HOVINGA et al. (1978) observed consistently higher blood pressures in the supine than in the left lateral position.
GINSBURG and DUNCAN (1969) suggested caval compression as the cause of the postural changes they observed. HOVINGA et al. (1978) considered the postural changes to be minor, finding that larger changes were evoked by conversation and noise. In the study of HOVINGA et al. (1978), the strain gauge was fixed at the level of the midpoint of the antero-posterior diameter of the chest in the supine position, and re-leveling of the gauge with position change was not described. The position of the strain gauge in the study of GINSBURG and DUNCAN (1969) was not stated at all. Thus, in these two studies, positional hydrostatic pressure differences between catheter tip and strain gauge were, presumably, not compensated for.

Thus, our results are in general agreement with most of the findings in the literature, that hydrostatic pressure gradients are responsible for at least the major part of the higher blood pressures measured in supine position in comparison to those in the left lateral position.
Other factors in addition to passive hydrostatic pressure differences may be operating in the hypertensive pregnant patients as is shown in section 8.2.3. The possible nature and mechanism of these factors will be dealt with later in this discussion.

To test whether the starting position, i.e. supine or left lateral, could influence the postural differences in blood pressure, different starting positions were employed in 10 pregnant patients. No differences were found according to whether the starting position was supine or left lateral, as described in section 8.1.2. This observation lends some further support to the concept that passive, hydrostatic pressure differences are important determinants of the positional blood pressure changes measured in this study. Since the first three measured blood pressures in either position were excluded, reflex-mediated blood pressure fluctuations during the period of initial adjustments to

the particular position were eleminated from consideration. Twenty minutes were considered to be adequate to achieve a stabile condition (SCHWARZ, 1964).
Also ESKES et al. (1974) demonstrated that the starting positions had no statistically significant influence upon the calculated postural difference in blood pressure in 17 serially studied pregnant women.

The investigators who have performed the "roll-over" test (see section 6.5), have measured the basal blood pressures in the left lateral position (after 20 minutes) and then again immediately and five minutes after turning the patient to the supine position. Thus, short-term blood pressure reactions to position change (and, indeed, to voice command and other external stimuli) have probably contributed more importantly to their results than have steady-state blood pressure levels. No author, however, has ever investigated the supine as the starting position for the "roll-over" test.

Only intra-arterial blood pressure measurements can give precise values for blood pressure (direct method, see section 1.2.1). The technique of measuring the blood pressure by Doppler ultrasound is, however, probably the most reliable of the indirect methods (see section 1.2.2.4). This is in part due to the automated principle of the device used, the Arteriosonde$^{R}$ (see section 7.1.3), whereby many operator and observer errors are excluded (see section 1.3.B). Even with this method, a certain degree of lack of precision in determining the blood pressure remains, and this must be kept in mind in analyzing the present data.

In the present study, assessment of the measurement errors in eight non-pregnant control subjects indicated that these were about 5 mmHg in the postural blood pressure determinations (see section 8.1.3).
The relatively large measurement error of 5 mmHg is obtained in spite of all possible precautions to reduce the measurement error, such as standardized conditions of the patients during blood pressure readings, averaging 9 blood pressure values and automated

blood pressure determinations. This measurement error also includes biological variations, such as minute-to-minute and circadian variations in blood pressure (SCHMIDT, et al., 1974). This implies that the method may be useful for the comparison between patient groups but not for individual subjects.

"Roll-over" tests are performed and analyzed in individual patients. A rise of more than 20 mmHg in the diastolic blood pressure in the supine position when compared with the blood pressure value in the left lateral position is called positive (GANT et al., 1974b). This positive test has been claimed to be a predictive sign for the development of hypertension later in pregnancy. Two blood pressure readings were considered precise enough to predict the development of pregnancy induced hypertension. However, in view of the imprecision of indirect blood pressure determinations, the differences in postural blood pressure change between observations lie within the error of the method. Therefore, this technique is perhaps not to be trusted in clinical practice.

In a preliminary study (VAN DONGEN and ESKES, 1979) of 69 primigravidae and 75 control subjects it appeared that higher basal blood pressures were associated with greater postural blood pressure differences. Normotensive pregnant women showed larger postural blood pressure changes than non-pregnant controls; and hypertensive pregnant women (defined by a mean arterial blood pressure of more than 105 mmHg in supine position) had larger postural blood pressure differences than normotensive patients.

Four tentative conclusions were thus suggested by this pilot study:

1. Hypertension is associated with enhanced postural difference in blood pressure;
2. Pregnancy is associated with enhanced postural blood pressure difference ;
3. Hypertension in pregnancy is associated with further enhancement of postural blood pressure difference ;
4. There is no association between postural blood pressure

difference and foetal growth retardation.

In the present study, the number of subjects is nearly double that of the pilot study. The conclusions of that study may now be re-examined in the light of larger numbers, and also with separation into 3 groups on the basis of defined clinical criteria (see section 7.3.1).

To investigate further the first conclusion listed above statistical analyses were performed between the absolute blood pressure levels and the postural differences in both systolic and diastolic pressures. The correlation coefficients (Pearson) between the systolic and diastolic blood pressures in supine position and their respective postural differences had a positive sign in 9 of the 10 correlation coefficients (Table 8.2.1.A). Four of them were also statistically significant ($p<0.05$). This led to the conclusion that rising blood pressures give higher postural blood pressure differences.
However, all the blood pressures in the left lateral position were negatively correlated with their respective postural blood pressure differences, as is shown in Table 8.2.1.B. Five of the 10 correlations showed also statistically significant correlations.

This implies that the results are contradictory, depending on the starting positions. This situation cannot actually exist, however, since the supine and left lateral blood pressures were highly and positively correlated with one another. An explanation of this phenomenon was found in the influence of the error in the initial value in the measured blood pressures in the supine position.
If one assumes that the positional differences in blood pressure are unrelated to the absolute level of resting blood pressure, then it will be apparent that, since the blood pressure measured in the supine position was in almost all instances greater than that found in the lateral position, an overestimate (positive error) of a blood pressure parameter in the supine position would tend to produce a greater apparent positional blood pressure difference. An underestimate (negative error) in a blood pressure measurement in the lateral position would also lead to a large

apparent positional blood pressure difference. Conversely, an underestimate of the supine blood pressure, or an overestimate of the lateral blood pressure, would tend to yield smaller positional differences.
Thus, measurement errors which are relatively large in comparison to the absolute differences in the parameters being measured would tend to bias the results so as to produce just the sort of statistical correlations observed here: a positive correlation of the difference with a higher supine blood pressure, and a negative correlation with a higher lateral blood pressure.
To remove systematic influences of the measurement errors in this case, the average systolic and diastolic blood pressures were calculated (see section 7.1.3). These showed indeed no significant correlation coefficients (Table 8.2.1.C).

Thus, our preliminary results, which demonstrated that rising blood pressures were accompanied by rising postural blood pressure differences, were influenced by the phenomenon of the relatively high error in the initial value.

This initial value error is often encountered, but often neglected due to the absence of knowledge of this subject. If an initial value is high, the chance that some derived values are also high is more likely than if the initial value was low (VAN 'T HOF, 1977). The example that the higher one stands, the further one may fall, illustrates this problem.

The differences in blood pressure between those values obtained in supine and left lateral positions were thus unrelated to basal blood pressures in both non-pregnant and pregnant subjects. The tentative conclusion that hypertension is associated with enhanced postural blood pressure differences, must therefore be dismissed.

The present study also failed to substantiate the second conclusion of the preliminary study.
Earlier in this discussion it was pointed out that no significant differences in postural blood pressure changes were found between *normotensive* gravidae and non-pregnant control subjects.
In the preliminary study, subjects were divided into "normotensive"

and "hypertensive" categories according to a calculated mean arterial blood pressure (ultrasound) below or above 105 mmHg. Thus, some patients clinically diagnosed as hypertensive (and thus falling into group 2b or 2c in the present analysis) were included in the "normotensive" group of the preliminary study. The clearer definition of normotension in the present study thus yielded a "cleaner" study group, with the result that the apparent enhancement of postural blood pressure difference by pregnancy was found not to occur.

In summary, neither hypertension nor pregnancy alone gave rise to increasing postural blood pressure differences.

The third tentative conclusion of the pilot study was that hypertension in pregnancy is associated with enhanced postural blood differences. The phenomenon of the error of the initial value plays here also an important role.

Since in the present study other definitions of hypertension were used, it would appear from first inspection of Tables 8.2.2.2.B and 8.2.3.A that this conclusion must also be rejected, for the analysis of variance showed no significant differences among the three normotensive and three pregnant groups in $\Delta S$, $\Delta D$ or $\Delta M$.

In the two hypertensive groups, however, the positional change in diastolic blood pressure was greater than that in systolic blood pressure. Whereas the systolic blood pressure decreased only about 12 mmHg in turning from supine to the left lateral position, diastolic blood pressure decreased sbout 18 mmHg. Thus, the pulse pressure was smaller in the supine than in the left lateral position in the hypertensive patients. $\Delta P$ in these groups was -6.7 and -5.1 mmHg, respectively. In both hypertensive groups the $\Delta P$ was significantly different from zero (Table 8.2.3.A). The positional changes in systolic blood pressure in the two groups of hypertensive gravidae were very close to those expected from hydrostatic pressure changes, as discussed earlier; but the $\Delta D$'s were about 1½ times this value, and this difference between $\Delta S$ and $\Delta D$ was significant in both groups.

Thus, there weredifferences in blood pressure response to

position change between the non-pregnant control and normotensive pregnant groups on the one hand, and the two hypertensive groups on the other.

The present results differ from the two studies in the literature which report data comparing positional blood pressure changes between normotensive and hypertensive gravidae. LIM and WALTERS (1976) reported no significant differences in postural blood pressure change between normotensive and hypertensive pregnant patients; however, their data seem to show a tendency toward a wider pulse pressure in the supine position than in the lateral position in the six hypertensive patients studied, a finding at variance with the present results. Also in the study of LIM and WALTERS (1976) the resting blood pressure was higher in the lateral than in the supine position. These authors do not report the site of blood pressure determination, making the interpretation of these observations difficult.
In the other study, GINSBURG and DUNCAN (1969), using intra-arterial catheters, found no differences in postural blood pressure changes between 16 normotensive and 24 hypertensive patients studied at a duration of pregnancy of 34 weeks. These authors also report higher blood pressures in the left lateral position than in the supine position; however, they failed to note the position of the strain gauge which measured blood pressure, again rendering interpretation of baseline blood pressures uncertain. Thus, there is clearly no unaminity of findings with regard to differences in postural blood pressure change between normotensive and hypertensive gravidae. Methodologic differences between the two published studies and the present one, and also the incomplete reporting of methodologic details in the published studies make it impossible to explain the differences in results.

The mechanism which probably accounts for the greater postural difference in diastolic blood pressure in comparison with the postural difference in systolic blood pressure in our hypertensive pregnant subjects is a vasoconstrictor response to the supine position.

Chapter 6 dealt with the work of various authors on the subject of vascular reactivity in pregnant subjects. There, it

was noted that normotensive gravidae showed only minor alterations in pressor responsiveness to both epinephrine and norepinephrine (RAAB et al., 1956) but markedly decreased responsiveness to AII (ABDUL-KARIM and ASSALI, 1961; CHESLEY et al., 1965; TALLEDO et al., 1966) as compared with non-pregnant subjects.

The sensitivity to autonomic blockade in supine position was greatly enhanced (BRUST et al., 1948; ASSALI and PRYSTOWKSY, 1950) due to venous pooling in the legs. The inferior vena cava is compressed by the gravid uterus when the patients lies in the supine position (SCOTT and KERR, 1963; KERR et al., 1964; KERR, 1965; LEES et al., 1967). The resulting decrease in venous return to the heart is followed by a fall in cardiac output. In patients with well developed collateral venous circulation, no supine hypotensive syndrome occurs (SCOTT and KERR, 1963; KERR et al., 1964). However, when the sympathetic tone has been removed by autonomic blockade, vena caval compression greatly increases the venous pooling and the supine hypotensive syndrome develops (see also section 4.1).

Patients with essential hypertension during pregnancy react as normotensive women.
However, pre-eclamptic patients reacted markedly less to autonomic blockade than did non-hypertensive or hypertensive gravidae, suggesting that the vascular tone was maintained by non-neurogenic mechanisms (BRUST et al., 1948; ASSALI and PRYSTOWSKY, 1950).

Pre-eclamptic patients reacted to epinephrine, norepinephrine (ZUSPAN et al., 1964; TALLEDO et al., 1968) and angiotensin II infusions (TALLEDO et al., 1966; TALLEDO et al., 1968) with increased pressor responses as compared with normotensive or hypertensive pregnant patients.

In some gravidae, this enhanced sensitivity to AII is already present at 22 weeks' gestation (GANT et al., 1973) and is even further increased by salt loading (GANT et al., 1974a).
The subjects with this increased sensitivity to AII are destined to develop pregnancy induced hypertension (PIH) later in pregnancy (GANT et al., 1974b).
In these same gravidae, the MCR-DS (see section 6.2) also becomes decreased 4 weeks prior to the appearance of clinical evidence

of the PIH (GANT et al., 1971; WORLEY et al., 1978), suggesting that a decrease in uterine blood flow occurs before the development of clinical toxaemia (GANT et al., 1976). The MCR-DS has been shown to be essentially the same in both the left lateral and supine positions, suggesting that a position-sensitive homeostatic mechanism is operating to maintain the utero-placental perfusion (SINGLEY et al., 1976).

An utero-placental autoregulatory mechanism under circumstances of reduced cardiac output appears to be mediated by the local release of prostaglandins of the E-series, resulting in vasodilatation of the utero-placental vascular bed when diminished perfusion occurs (McGIFF et al., 1970; LONIGRO et al., 1973; SPEROFF, 1973; TERRAGNO et al., 1976)

The difference in responsiveness to angiotensin II infusions between toxaemic and pre-toxaemic gravidae and normal pregnant women is not related to differences in plasma levels of endogenous angiotensin II (GORDON et al., 1973). Rather, the explanation seems to lie in differences in sensitivity of the resistance vessels to the constrictor effects of angiotensin II (GANT et al., 1973, 1974a, b). EVERETT and co-workers have recently shown that the pressor responsiveness to angiotensin infusions can be enhanced by prostaglandin synthetase inhibitors (EVERETT et al., 1978b) and decreases by 5-α-dihydroprogesterone (EVERETT et al., 1978a). Locally produced E-series prostaglandins are known to be potent dilators in many vascular beds (BRODY and KADOWITZ, 1974), and modulation of prostaglandin production by steroid hormones has been demonstrated in the placenta and endometrium of several species (THORBURN et al., 1977).

Thus, differences in vascular reactivity between non-pregnant subjects, normotensive gravidae, gravidae with hypertension predating pregnancy and women with pregnancy induced hypertension may reflect subtle differences in endocrine modulation of local prostaglandin-mediated mechanisms of vascular control.

Our findings of a greater positional change in diastolic than in systolic blood pressure with the two groups of hypertensive gravidae are in general agreement with the prevailing concept in

the literature that vascular reactivity is enhanced in patients with pregnancy induced hypertension. Our patients with pre-existing hypertension (2b) demonstrated aggravation of the hypertension and other evidence of super-imposed toxaemia.

The supine position is thus one of the stimuli of vasoconstriction

Earlier in this discussion it was stated that the decreased circulating blood volume in the supine position is caused by compression of the inferior vena cava by the gravid uterus. The positional decrease in effective blood volume may be aggravated in hypertensive gravidae, for these patients have smaller blood volumes than normotensive gravidae.

ARIAS (1975) determined blood volumes in three non-hypertensive subjects, four others with pregnancy induced hypertension, and 20 multiparous patients with hypertension predating pregnancy. The blood volume in the non-hypertensive subjects was significantly greater than in the hypertensive patients of both sorts. Also, a significant correlation was found between the blood volume and foetal weight: the smaller the blood volume, the lower the foetal weight. A decrease in the pregnancy induced expansion of intravascular volume and not the degree of arterial vasoconstriction was thought to be the cause for these findings.

However, ASSALI and VAUGHN (1977) demonstrated clearly that, from the view point of haemodynamics, it must be the other way around: that smaller blood volume is the result of vasoconstriction. The smaller blood volume merely fits a contracted vascular bed in patients with pregnancy induced hypertension.

Three factors thus may act together to account for the greater positional change in diastolic as compared to systolic blood pressure in the hypertensive gravidae: diminished blood volume, vena caval compression in the supine position, and a reactive vascular bed. In the left lateral (neutral) position, the reduced blood volume fills a constricted vascular bed. When the effeftive blood volume is further reduced by vena caval compression in the supine position, the results are vasoconstriction (thus elevation in diastolic blood pressure) and

reduced cardiac stroke volume (thus a smaller change in systolic blood pressure).

These circulatory adjustments may be further accompanied by a decrease in utero-placental blood flow.
This diminished circulating blood volume reduces the stroke volume, and thus the systolic blood pressure, resulting in postural differences in systolic blood pressure which were similar in normotensive and non-pregnant subjects in our study groups. However, the postural differences in diastolic blood pressure were higher than the systolic parameters within the hypertensive groups. Pregnancy induced hypertension is thus accompanied by an increase of vasoconstriction. This in turn is responsible for the decrease in uteroplacental blood flow.

Since hypertension during pregnancy is associated with an increased incidence of poor intrauterine foetal growth, (ARIAS, 1975, DUNLOP, 1966), we tried to find a connection between the evidence of enhanced vascular reactivity and the occurrence of foetal growth retardation in our study subjects.

A weak but significant negative correlation (Pearson) between birth weight percentile and $\Delta S$ and $\Delta M$ was found (Table 8.2.4.A). Multiple regression analysis between birth weight percentile, absolute blood pressures and postural blood pressure differences also revealed a significant negative correlation between birth weight percentile and $\Delta S$ and $\Delta M$, apart from the correlation between the absolute blood pressures and the birth weight percentiles.
If the subjects were dichotomized into those with and without growth retarded infants, no differences were found in any of the mean postural blood pressure differences between the subgroups thus created (Table 8.2.4.B). Therefore, the $\Delta S$-birth weight percentile correlation appears to result from overall birth weight distribution and not particularly from the dysmature category.

Several possibilities were considered in attempting to explain this relationship between postural differences in systolic blood pressure and infant birth weight percentile.

First was the possibility that the effect might be related to

the size of the mother: large mothers tend to have larger infants (THOMSON et al., 1968), and also larger women would tend to have greater arm-heart distances and thus wider hydrostatic positional blood pressure differences. This possibility was discarded, for the observed correlation was a negative one, and not positive as would be predicted if maternal size were the determinant.

The second factor considered as a possible cause of this correlation between the postural differences in systolic blood pressure and the birth weight percentile was measurement error. As seen earlier, duplicate errors were about 5 mmHg (see section 8.1.3). However, we could find no reason why a systematic bias should occur in the postural blood pressure difference of systolic blood pressure (and not in the diastolic blood pressure) related to pregnancy outcome. Thus, this possibility was also discarded.

A possible explanation for this phenomenon might be that the size (weight) of the foetus affects the magnitude of $\Delta S$, and not the reverse. In our subjects, the systolic blood pressure was generally higher in the supine than in the left lateral position. Decreased effective blood volume in supine position as a result of vena cava compression would tend to lower cardiac stroke volume, and thus decrease supine systolic blood pressure. Therefore, the greater the supine circulatory impairment, the lower the $\Delta S$, and the reverse.
The larger the foetus, the larger also the uterus, and the more the resulting compression of the inferior vena cava in the supine position. Thus, a smaller $\Delta S$ would be expected with the subjects who were carrying larger foetus as compared with normal or small foetus.

It is well known that rising blood pressures cause an enhanced perinatal morbidity and mortality. The work of various authors has been described in chapter 5 and a summary of the perinatal mortality rates is given in Table 5.2.

Our findings with regard to resting blood pressures are in accordance with these well-accepted earlier findings. In the group of patients who developed PIH (group 2c), 4 of 6 resting blood pressure parameters were higher in patients who later

delivered dysmature infants (Table 8.2.4.B). There were also significant negative correlations between resting blood pressure parameters and birth weight percentile (Tables 8.2.4.A and 8.2.4.C).

According to most observers, hypertension with proteinuria has been associated with a poorer foetal outcome than hypertension without proteinuria (McCLURE BROWNE, 1961; BUTLER and ALBERMAN, 1969; TERVILÄ et al., 1973; PAGE and CHRISTIANSON, 1976b; FRIEDMAN and NEFF, 1976, 1978). Not only is the foetal morbidity and mortality increased, but also the incidence of foetal growth retardation is greater when proteinuria accompanies elevated blood pressure (TERVILÄ et al., 1973; PAGE and CHRISTIANSON, 1976a, 1976b).

Possible relationships between proteinuria and blood pressure parameters were statistically analyzed in the present study as well; however, the presence or absence of proteinuria did not affect the blood pressure parameters or incidence of dysmaturity in our groups. The explanation for this might be that the number of subjects was small : 18 in the PIH-group and 28 in total. A further explanation lies in the definition of proteinuria used in the University Hospital, Nijmegen (Dept. Obstetrics & Gynaecology): >150 mg/24 hrs. PAGE and CHRISTIANSON (1976b) considered proteinuria to be positive above 1000 mg/1000 ml. The Committee on Terminology of the American Committee on Maternal Welfare (CHESLEY, 1978) considered the loss of protein above 500 mg/24 hrs as a reasonable criterion for the diagnosis proteinuria.
If the dividing line for proteinuria is set at 500 mg/24 hrs, then only three patients in the present study group meet this definition, a very small number indeed for further analysis.

Earlier in this discussion statements on the roll-over tests were made. Various authors considered the roll-over test or supine pressor test or supine hypertensive test as a useful clinical test to predict PIH, when the test was performed between the 28th and the 32nd week of pregnancy. The work of these authors is described in section 6.5 and summarized in Table 6.5.

GANT et al. (1974b) found in normotensive nulliparous subjects

who showed an enhanced reaction to the infusion of angiotensin II between the 28th and the 32nd week of pregnancy, that the diastolic blood pressure rose more than 20 mmHg when they were turned from the left lateral to the supine position. The blood pressures in left lateral position were measured after 20 minutes of rest. The blood pressures in supine position were determined immediately after turning and 5 minutes later. The highest value of these two measurements was considered in scoring the test as negative or positive. Ninety-three percent of those women who showed the enhanced reaction to position change also developed PIH later in pregnancy (see Table 6.5), in contrast to only 9% PIH in women who showed a postural diastolic blood pressure increase of less than 20 mmHg.

In our discussion on measurement errors it was noted that the indirect auscultatory method of blood pressure measurement used by GANT et al. (1974b),and also by most authors who have reported "roll-over" results, is imprecise because of the magnitude of the measurement error. The differences in postural blood pressure change between observations lie within the error of the method Moreover, the data given by GANT et al. (1974b) shows an almost uniform high incidence of diastolic blood pressure values with a zero-end-digit. This means that steps of 10 mmHg were taken in the estimation of the blood pressure (auscultatory method). It is thus quite possible that prejudice, observer bias and zero-end-digit preference influenced the found postural differences in blood pressure as much as the actual blood pressure change itself.

However, the test was so attractive that investigations were carried out by 9 other investigators. Table 6.5 shows the results of these studies. In most cases, the authors concluded that the "roll-over" test identifies to some extent those gravidae at increased risk for hypertension later during pregnancy. The negative test, however, has a greater predictive value for the absence of PIH than the positive test shows for the presence of this complication.

The roll-over test is derived from the diastolic blood pressure. However, TERVILÄ (1978, personal communication), stated that the systolic blood pressure change was significantly predictive for

the development of PIH, whereas the diastolic blood pressure change was not predictive at all.

O'GRADY et al. (1977) used an ultrasound automated device. Observer bias and digit preferences were thus excluded. This longitudinal study in 24 primigravidae between the 27th and the 35th week of pregnancy demonstrated a great variability between positive and negative tests from week to week in individual subjects. The blood pressure in the left lateral position was calculated as the mean of 7 measurements made during half an hour. These values were compared with the highest of the two blood pressure values obtained in the supine position (see section 6.5). If a dividing point for $\Delta D$ was set at 20 mmHg, then 17 of the 24 subjects had both positive and negative tests. Six of the 24 subjects had persistently negative tests, and only one patient showed consistently positive tests. This patient did not develop PIH. A single positive or negative test was therefore not predictive. Patients with persistently negative "roll-over" tests did not develop PIH.

However, although the "roll-over" test in an individual patient may not be considered to be of predictive value as to the development of PIH, the possibility should not be ruled out that patients who will develop or have developed PIH, show an enhanced vascular reactivity to several kinds of stimuli. The supine position could be one of them.

For obvious methodologic reasons, our results are not comparable with those obtained with the "roll-over" tests. Moreover, in this cross-sectional study an exaggerated response in vascular reactivity was found in those patients who had already developed PIH, whereas the roll-over test was "designed" as a predictive instrument.

Twelve volunteers agreed to have blood pressures studied by the methods already described (see section 7.3.2) during pregnancy and four days and six weeks post partum. The clinical features of each individual patient are summarized in Tables 9.A, 9.B and 9.C. Note that his group of patients may not be considered to be a representative sample of a well-defined pregnant population. Therefore, the statistical analyses are limited to the description of individual features and a few general tendencies.

The quality of the longitudinal measurement methods is discussed in section 9.1, whereas the pattern of the postural differences in blood pressure during pregnancy in the 12 subjects studied is given in section 9.2.

## *9.1 Control of measurement methods*

ARMITAGE and ROSE (1966) demonstrated downward trends in both systolic and diastolic blood pressure levels in non-pregnant individuals who were checked daily by the same investigator during 6 weeks (see section 3.3). They suggested that the decrease in blood pressure is mainly due to the patient's acclimatisation to observer, apparatus and environment. Because this so-called "test effect" is often met in longitudinal studies (VAN 'T HOF, 1977), the influence of this factor was analyzed in our longitudinal study. We assumed that the first two and the last measurements (six weeks post partum) are not affected by pregnancy, but the last value may include such a test effect. Therefore, the difference between the average value of the two first measurements and the last measurement is considered to be a good estimate for a possible test effect. The results are presented in Table 9.1.

TABLE 9.A PARTICULARS OF THE LONGITUDINAL PATIENTS BEFORE THE PREGNANCY STUDIED

| Patient | Weight (kg) | Height (cm) | Q.I. ($kg/cm^2$) | Remarks (including former pregnancies) |
|---|---|---|---|---|
| PK 131146 | 58 | 163 | 21.8 | Argonz del Castillo; bromocriptine (4 abortions); bromocriptine+ clomiphene |
| HS 251152 | 66 | 176 | 21.3 | Oligomenorrhoea (clomiphene+HCG) |
| DB 170848 | 53 | 160 | 20.7 | Pyelonephritis (PHT*); one abortion |
| TO 260656 | 73 | 176 | 23.5 | PHT (essential; familial) |
| TK 250952 | 57 | 171 | 19.4 | Oligomenorrhoea (clomiphene+HCG) |
| HJ 051152 | 59 | 162 | 22.4 | Polycystic ovary disease (clomiphene, HMG, HCG, wedge resection: one abortion); tamoxifene |
| SH 220348 | 72 | 160 | 28.1 | Glomerulonephritis (PHT); c.s. (pre-eclampsia) |
| BJ 171154 | 56 | 159 | 22.1 | Intrauterine foetal death (placental insufficiency); PHT |
| ML 050248 | 63 | 156 | 25.8 | Three abortions; one intrauterine foetal death (placental insufficiency); PHT (chlorthalidone, propranolol) |
| BB 120741 | 58 | 170 | 20.0 | Postural proteinuria during 1st pregnancy |
| PA 050449 | 53 | 163 | 19.9 | Oligomenorrhoea |
| KD 140454 | 66 | 160 | 25.7 | Immature delivery (17 weeks); no uterine anomaly; PHT |

* : PHT, pre-existing hypertension

TABLE 9.B PARTICULARS OF THE LONGITUDINAL PATIENTS DURING THE PREGNANCY STUDIED

| Patient | Age (yr) | Pregnancy | Parity | Wt-gain (kg) | Diet from (weeks)* | Medication** | Remarks |
|---|---|---|---|---|---|---|---|
| PK 131146 | 31 | 5 | 0 | 9 | Na/CHO (6) | insulin | No HT; diabetes gravidarum (Na)***; pos.disc. 25th wk |
| HS 251152 | 26 | 1 | 0 | 11 | Na (33) | - | No HT; neg.disc. 33rd wk (Na) |
| DB 170848 | 30 | 2 | 0 | 7 | Na (8) | - | HT (Na); neg.disc. 33rd wk |
| TO 260656 | 22 | 1 | 0 | 12 | Na (9) | - | HT (Na); uneventful |
| TK 250952 | 26 | 1 | 0 | 9 | Na (29) | - | No HT; wt-gain↑(Na); proteinuria 36th wk |
| HJ 051152 | 26 | 2 | 0 | 10 | Na (38) | - | No HT; wt-gain↑(Na) |
| SH 220348 | 30 | 2 | 1 | 7 | Na (8) | - | HT (Na); bacteriuria 22nd wk(Kl.pneumoniae); neg.disc.36th wk; pre-eclamptic complaints |
| BJ 171154 | 23 | 2 | 1 | 7 | Na (7) | - | No HT; PHT (Na); neg.disc. 35th wk; blood loss 36th wk (placental abruption) |
| ML 050248 | 30 | 6 | 2 | 5 | Na (6) | α-methyl dopa (tid 250 mg) | HT (Na); hypertensive crises after 31st wk |
| BB 120741 | 37 | 2 | 1 | 6 | Na (17) | - | HT since 17th wk (Na); no proteinuria |
| PA 050449 | 29 | 2 | 1 | 11 | - - | - | No HT; uneventful |
| KD 140454 | 34 | 2 | 1 | 7 | Na/CHO (6) | insulin | HT; diabetes gravidarum (Na) |

* Na : sodium restricted diet ( <20 mmol/24 hrs) CHO : carbohydrate-enriched diet

** Ferrous fumarate routinely prescribed to all patients

*** Reason of administering sodium restricted diet

HT = hypertension

PHT = pre-existing hypertension

TABLE 9.C PREGNANCY OUTCOME OF THE LONGITUDINAL PATIENTS

| Patient | Birth Weight (g) | Gest.at deliv. (weeks) | Percen-tile birth wt | Sex of infant | Wt of placenta* (g) | Remarks |
|---|---|---|---|---|---|---|
| PK 131146 | 4100 | 41 | 95-97.7 | F | 460** | Meconium stained amniotic fluid |
| HS 251152 | 2820 | 39 | 10-25 | F | 460 | Placenta circumvallata |
| DB 170848 | 2090 | 37 | 5-10 | M | 250** | Premature rupture of membranes |
| TO 260656 | 3680 | 41 | 75-90 | F | 650 | Uneventful |
| TK 250952 | 3680 | 42 | 50-75 | M | 390 | Forceps (bradycardia) |
| HJ 051152 | 3030 | 40 | 10-25 | F | 430 | Forceps (second stage of labour: one hour) |
| SH 220348 | 2890 | 40 | 10-25 | F | 430** | Forceps (bradycardia) |
| BJ 171154 | 1880 | 36 | 2.3-5 | M | 270** | Caesarean section (partial placental abruption) |
| ML 050248 | 2400 | 37 | 10-25 | F | 350 | Caesarean section (hypertensive crises; low oestriol excretion) |
| BB 120741 | 3820 | 41 | 50-75 | M | 600 | Induction of labour (ocytocin) |
| PA 050449 | 2950 | 38 | 10-25 | M | 400 | Uneventful |
| KD 140454 | 3260 | 41 | 10-25 | M | 360 | Manual removal of placenta (retained placenta) |

* : Weight of placenta without membranes and umbilical cord

** : Placental infarcts

TABLE 9.1 COMPARISON BETWEEN THE AVERAGE OF THE TWO INITIAL BLOOD PRESSURE LEVELS AND THE LEVEL SIX WEEKS POST PARTUM (PP)

| | Systolic | | Diastolic | |
|---|---|---|---|---|
| Patient | Initial* | 6 wks pp | Initial* | 6 wks pp |
| PK 131146 | 111 | 120 | 69 | 68 |
| HS 251152 | 121 | 111 | 58 | 53 |
| DB 170848 | 121 | 118 | 67 | 76 |
| TO 260656 | 123 | 125 | 73 | 81 |
| TK 250952 | 116 | 121 | 59 | 72 |
| HJ 051152 | 110 | 123 | 60 | 76 |
| SH 220348 | 145 | 125 | 83 | 73 |
| BJ 171154 | 113 | 114 | 65 | 56 |
| ML 050248 | 123 | 134 | 94 | 103 |
| BB 120741 | 114 | 108 | 71 | 70 |
| PA 050449 | 108 | 95 | 65 | 65 |
| KD 140454 | 130 | 115 | 78 | 80 |

* Mean value of the two first blood pressure measurements

In six patients the initial systolic blood pressure values were lower and in six higher than the last non-pregnant values. In five patients the initial diastolic blood pressure values were higher and six lower than the last non-pregnant values. Comparable results were obtained when the first blood pressure readings during pregnancy were compared with the non-pregnant values.
Thus, a test effect upon either the systolic or diastolic blood pressure value could not be demonstrated in this study, and this effect may be neglected in further analyses.

*9.2 Postural differences in blood pressure*

The postural differences in systolic ($\Delta S$), diastolic ($\Delta D$) and

TABLE 9.2.A POSTURAL DIFFERENCES IN BLOOD PRESSURE OF THE LONGITUDINAL PATIENTS DURING PREGNANCY

| Patient | | ΔS | | | | | ΔD | | | | | ΔP | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n** | Min. | Mean | Max. | SD | Slope*** | Min. | Mean | Max. | SD | Slope | Min. | Mean | Max. | SD | Slope |
| PK 131146 | 18 | 9 | 15 | 24 | 3.9 | 0.1 | 12 | 20 | 27 | 4.2 | 0.3* | -14 | -5 | 4 | 4.6 | -0.2 |
| HS 251152 | 17 | 2 | 16 | 31 | 6.8 | -0.0 | -1 | 13 | 30 | 8.1 | 0.3 | -16 | 3 | 22 | 10.8 | 0.3 |
| DB 170848 | 13 | 6 | 12 | 17 | 3.3 | -0.0 | 9 | 14 | 25 | 4.5 | 0.1 | -19 | -2 | 4 | 6.0 | -0.1 |
| TO 260656 | 16 | 0 | 11 | 20 | 6.3 | -0.0 | 12 | 19 | 28 | 4.6 | 0.2 | -14 | -8 | 0 | 4.2 | -0.2 |
| TK 250952 | 19 | 4 | 13 | 20 | 3.7 | -0.2* | 10 | 19 | 26 | 5.3 | 0.3* | -22 | -6 | 6 | 7.3 | -0.5* |
| HJ 051152 | 18 | 3 | 15 | 33 | 6.0 | -0.1 | 7 | 21 | 29 | 7.2 | 0.7* | -18 | -6 | 26 | 11.2 | -0.8* |
| SH 220348 | 16 | 9 | 16 | 27 | 4.3 | -0.1 | 8 | 18 | 25 | 5.1 | -0.1 | -12 | -2 | 5 | 5.5 | -0.0 |
| BJ 171154 | 12 | 2 | 11 | 23 | 5.1 | -0.1 | 7 | 13 | 21 | 4.6 | 0.1 | -7 | -2 | 16 | 6.4 | -0.2 |
| ML 050248 | 16 | 1 | 9 | 30 | 7.1 | -0.2 | 5 | 13 | 22 | 5.9 | 0.0 | -11 | -4 | 8 | 6.7 | -0.3 |
| BB 120741 | 18 | 5 | 13 | 25 | 6.0 | -0.4* | 3 | 14 | 24 | 4.5 | 0.0 | -13 | -1 | 21 | 7.4 | -0.4* |
| PA 050449 | 12 | 8 | 13 | 21 | 3.5 | 0.1 | 8 | 14 | 19 | 3.9 | 0.2 | -6 | -1 | 8 | 4.2 | -0.1 |
| KD 140454 | 19 | 4 | 10 | 15 | 3.3 | 0.1 | 8 | 14 | 21 | 3.8 | 0.2* | -12 | -4 | 7 | 4.8 | -0.3* |

* Slope is significantly different from zero ($p<0.05$)

** Number of blood pressure recordings during pregnancy

*** Expressed in mmHg/week

pulse (ΔP) pressures during pregnancy (ultrasound method, see section 7.1.3) are given in Table 9.2.A and in the Figures 9.1 - 9.12.

In 11 patients the average ΔD-value is higher than the average ΔS-values. Thus, in these 11 patients, ΔP has a negative sign: i.e., pulse pressure was greater in the lateral than in the supine position. The sign test ($p<0.01$) indicates that this may be considered as a general phenomenon in our study group.

Regression lines of the ΔS,ΔD and ΔP as functions of the duration of amenorrhoea were calculated (see Table 9.2.A). Significant levels (regression analysis, $p<0.05$) in the individual slopes were reached two times for ΔS, four times for ΔD and four times for ΔP.

In the non-pregnant state at 4 days and 6 weeks post partum, respectively, the postural differences in the blood pressure parameters showed no consistent change when compared with the average pregnant levels: both lower and higher values can be seen (Table 9.2.B).

TABLE 9.2.B POSTURAL DIFFERENCES DURING PREGNANCY, FOUR DAYS AND SIX WEEKS POST PARTUM

| Patient | ΔS | | | ΔD | | | ΔP | | |
|---|---|---|---|---|---|---|---|---|---|
| | pregn.* | 4 days pp | 6 wks pp | pregn.* | 4 days pp | 6 wks pp | pregn.* | 4 days pp | 6 wks pp |
| PK 131146 | 15 | 15 | 11 | 20 | 17 | 21 | -5 | -2 | -10 |
| HS 251152 | 16 | 18 | 24 | 13 | 9 | 12 | 3 | 9 | 12 |
| DB 170848 | 12 | 16 | 8 | 14 | 11 | 11 | -2 | 5 | -3 |
| TO 260656 | 11 | 12 | 5 | 19 | 22 | 12 | -8 | -10 | -7 |
| TK 250952 | 13 | 11 | 19 | 19 | 12 | 20 | -6 | -1 | -1 |
| HJ 051152 | 15 | | 4 | 21 | | 24 | -6 | | -20 |
| SH 220348 | 16 | | 18 | 18 | | 8 | -2 | | 10 |
| BJ 171154 | 11 | | 5 | 13 | | 14 | -2 | | -9 |
| ML 050248 | 9 | 10 | 3 | 13 | 11 | 9 | -4 | -1 | -6 |
| BB 120741 | 13 | 12 | 5 | 14 | 13 | 3 | -1 | -1 | 2 |
| PA 050449 | 13 | 13 | 16 | 14 | 17 | 14 | -1 | -4 | 2 |
| KD 140454 | 10 | 16 | 16 | 14 | 5 | 15 | -4 | 11 | 1 |

* Mean values of Δ (see Table 9.2.A)

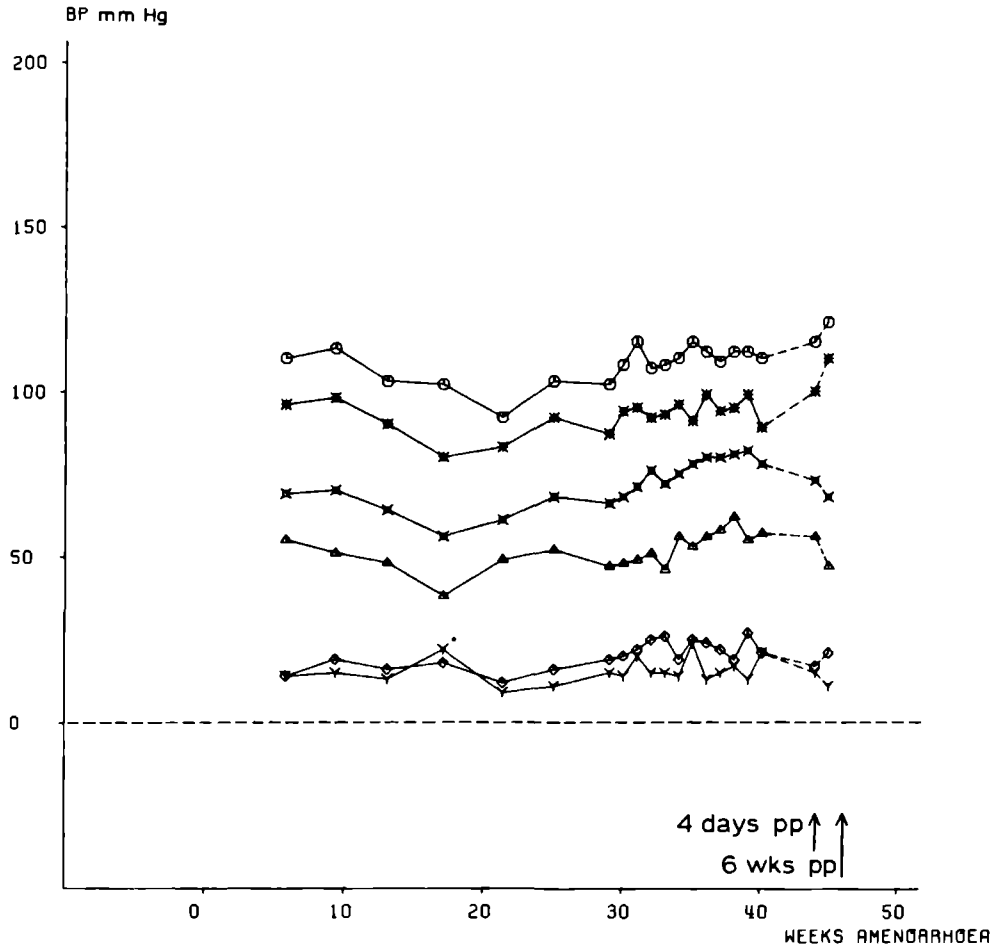
The patients in the longitudinal study did not, as a group, demonstrate major patterns of change in the postural blood pressure differences during the course of pregnancy. There was a slight tendency for ΔD to increase during pregnancy; however, this reached statistical significance in only four of the twelve patients. The ΔS exhibited a significant decreasing trend in two patients, with no consistent pattern in the remaining subjects. The positional change in pulse pressure tended to become increasingly negative (that is, narrower in the supine than in the left lateral position) in the majority of subjects, although this again was significant in only four individuals. These overall changes, though not striking, are compatible with the haemodynamic mechanisms discussed earlier (see section 8.3): increasing aortocaval compression leading to decreased cardiac stroke volume in the supine as compared with the lateral position, and compensated for (in some subjects, at least) by increased vasoconstrictor tone in the supine position.

The most striking features of the postural blood pressure differences in these 12 subjects are the range of values recorded in each parameter in each individual subject (Table 9.2.A), and the change in either direction which could be recorded between successive observations (Figures 9.1 - 9.12). These variations probably represent both real change in the physiologic state or reactivity of the patient, and measurement error. The relative contribution of each of these factors to the observed variations is difficult to assess; however, it should be noted that the standard deviations of the postural blood pressure differences (Tables 9.2.A) are in the same range as the duplicate error determined for the technique used (see section 8.1.3). The frequent, sizeable change in the magnitude of the postural blood pressure differences between successive observations is, moreover, in general agreement with the findings of O'GRADY et al. (1977), who reported that only a small minority of their serially-studied subjects exhibited ΔD's consistently above or below the 20 mmHg predictive line for pregnancy induced hypertension suggested by GANT et al. (1974b).

Although the methodology employed in this study was not the same as that used in the roll-over tests (GANT et al., 1974b and others - see Table 6.5 - ), the present findings certainly do not support the roll-over test as a predictor of subsequent blood pressure performance, particularly in the individual patient. For example, every one of the 12 subjects exhibited, at one time or another, a minimum $\Delta D$ of 12 mmHg or less, and all but one subject showed a maximum $\Delta D$ of greater than 20 mmHg. The highest mean $\Delta D$, 21 mmHg was observed in a patient (HJ 051152) who remained normotensive. The only one of the 12 subjects who developed pregnancy induced hypertension (BB 120741) showed a mean $\Delta D$ of 14 mmHg.

Similarly, in this small longitudinal study group, there was no indication that the postural blood pressure changes, serially measured, gave any prognostication of subsequent delivery of a growth retarded infant. The two patients (DB 170848 and BJ 171154) who had dysmature infants, could not be distinguished in any way from the remaining patients on the basis of any of the postural blood pressure changes, or the trends in these changes. One subject (DB 170848) was hypertensive during the pregnancy studied; the other patient (BJ 171154) had a history of hypertension, but was normotensive according to the stated criteria during the study. These results are, however, in keeping with the findings in the cross-sectional study that the associations between hypertension and dysmaturity and between postural systolic blood pressure change and dysmaturity, though statistically significant, are still sufficiently weak that they could be expected to have little predictive value for individual gravidae.

The general conclusion can be drawn that in measuring blood pressures in pregnant patients in the supine and left lateral positions, the postural differences in blood pressure found between observations lie within the error of the method. The method is thus not useful in the individual patient.




Blood pressures and postural BP differences by ultrasound method

SBP supine
SBP left lateral
ΔS
DBP supine
DBP left lateral
ΔD

Fig. 9.1 PK 131146

Secondary infertility (Argonz del Castillo). Four abortions, parity 0. No pre-existing hypertension, no hypertension during pregnancy, no dysmaturity, insulin.

$\overline{\Delta D} > \overline{\Delta S}$ (i.e. $\overline{\Delta P} < 0$).

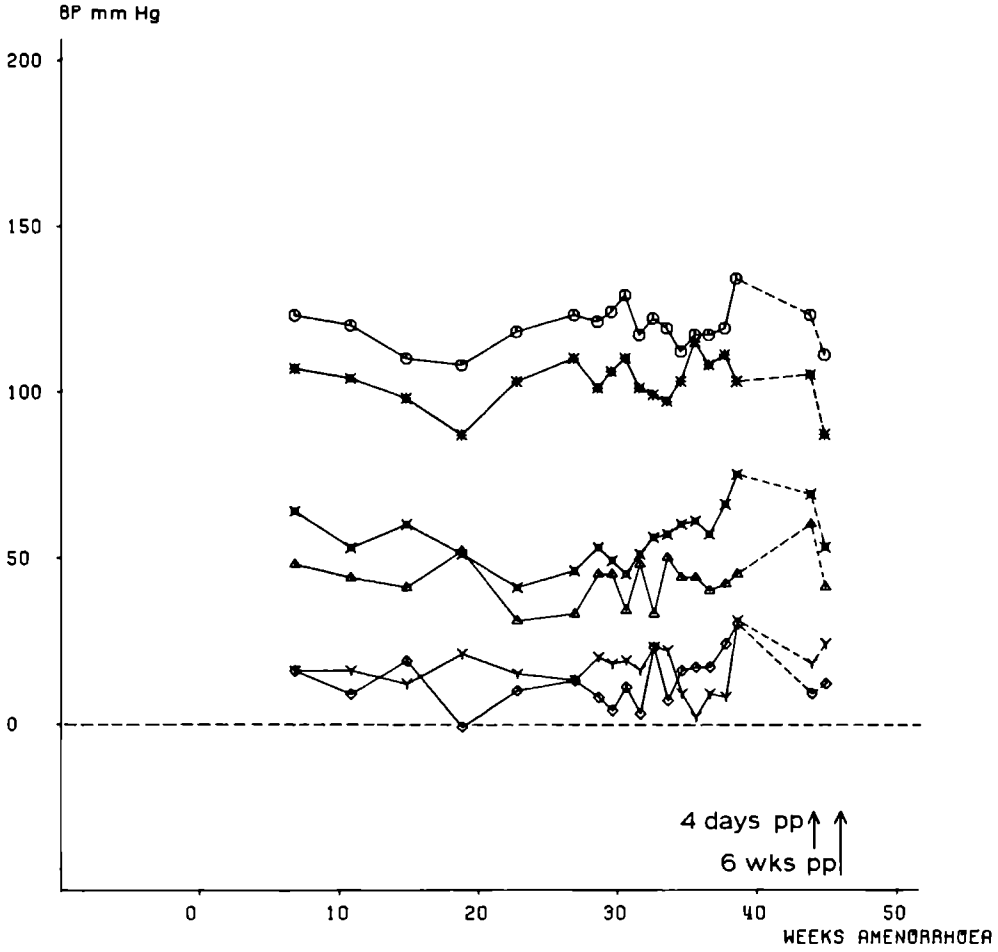
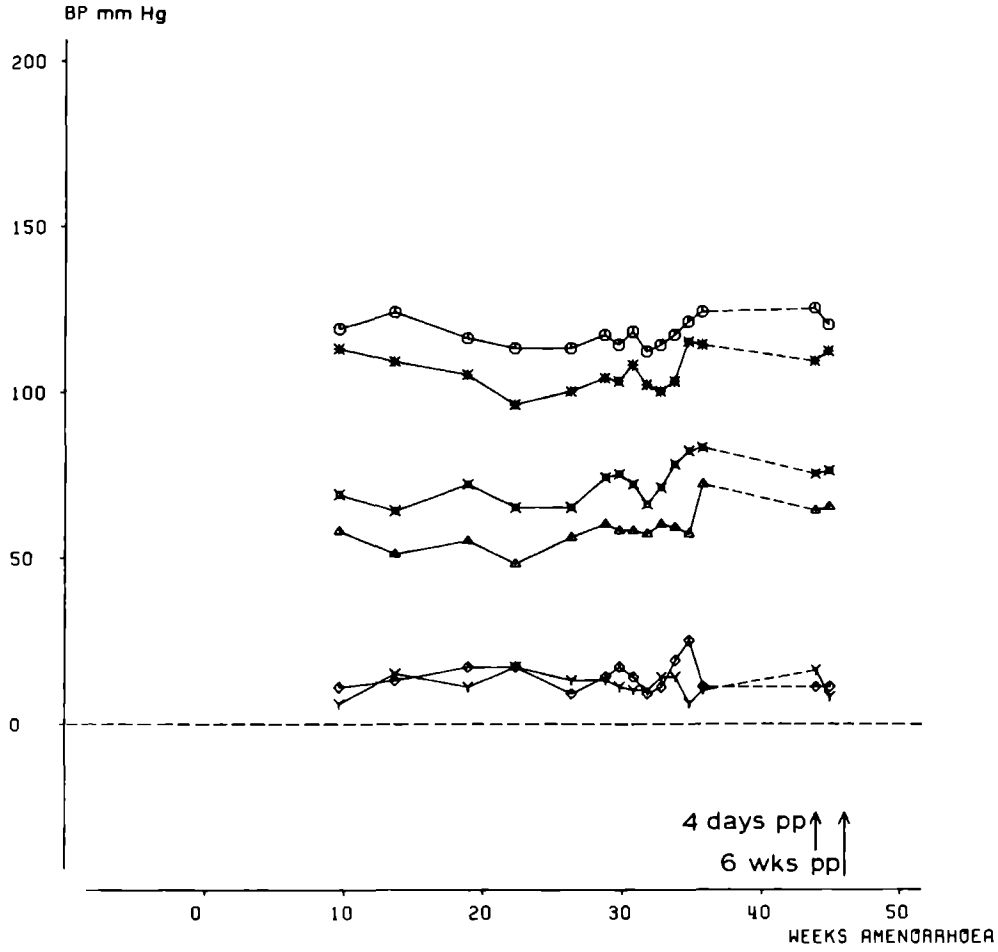



Fig. 9.2 HS 251152

Primary infertility. Parity 0. No pre-existing hypertension, no hypertension during pregnancy, no dysmaturity.

$\overline{\Delta S} > \overline{\Delta D}$ (i.e. $\overline{\Delta P} > 0$).




Blood pressures and postural BP differences by ultrasound method

SBP supine
SBP left lateral
ΔS
DBP supine
DBP left lateral
ΔD

Fig. 9.3 DB 170848

Pyelonephritis. One abortion, parity 0. Pre-existing hypertension, hypertension during pregnancy, prematurity and dysmaturity.

$\overline{\Delta D} > \overline{\Delta S}$ (i.e. $\overline{\Delta P} < 0$).

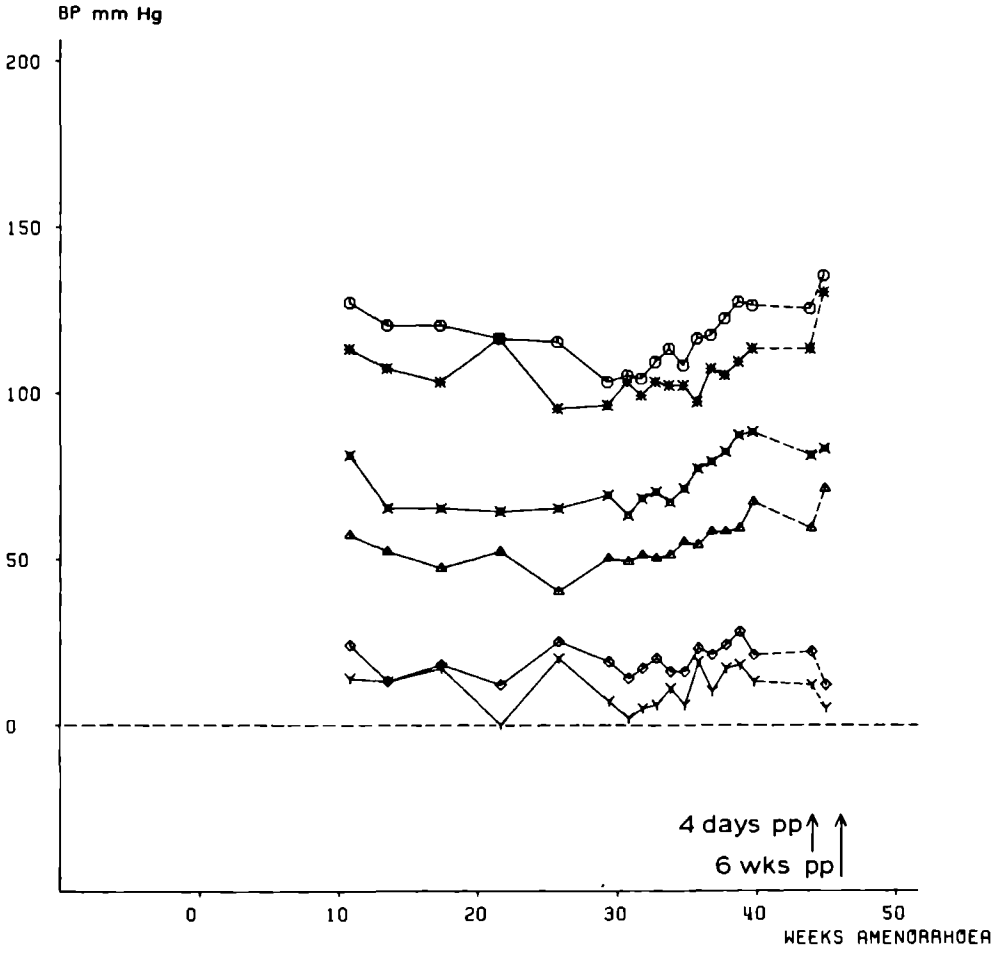



Fig. 9.4 TO 260656

Essential hypertension. Parity 0. Pre-existing hypertension, hypertension during pregnancy, no dysmaturity.

$\overline{\Delta D} > \overline{\Delta S}$ (i.e. $\overline{\Delta P} < 0$).

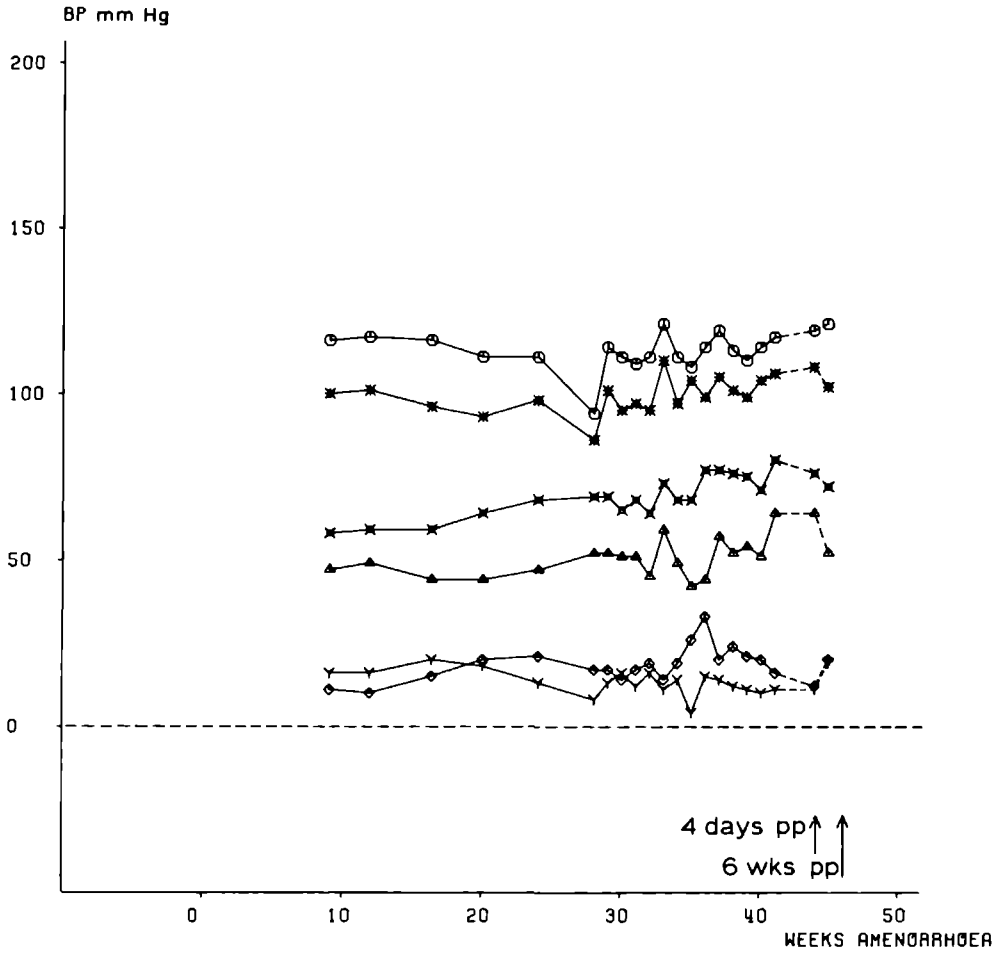



Fig. 9.5 TK 250952

Primary infertility. Parity 0. No pre-existing hypertension, no hypertension during pregnancy, proteinuria, no dysmaturity. $\overline{\Delta D} > \overline{\Delta S}$ (i.e. $\overline{\Delta P} < 0$).

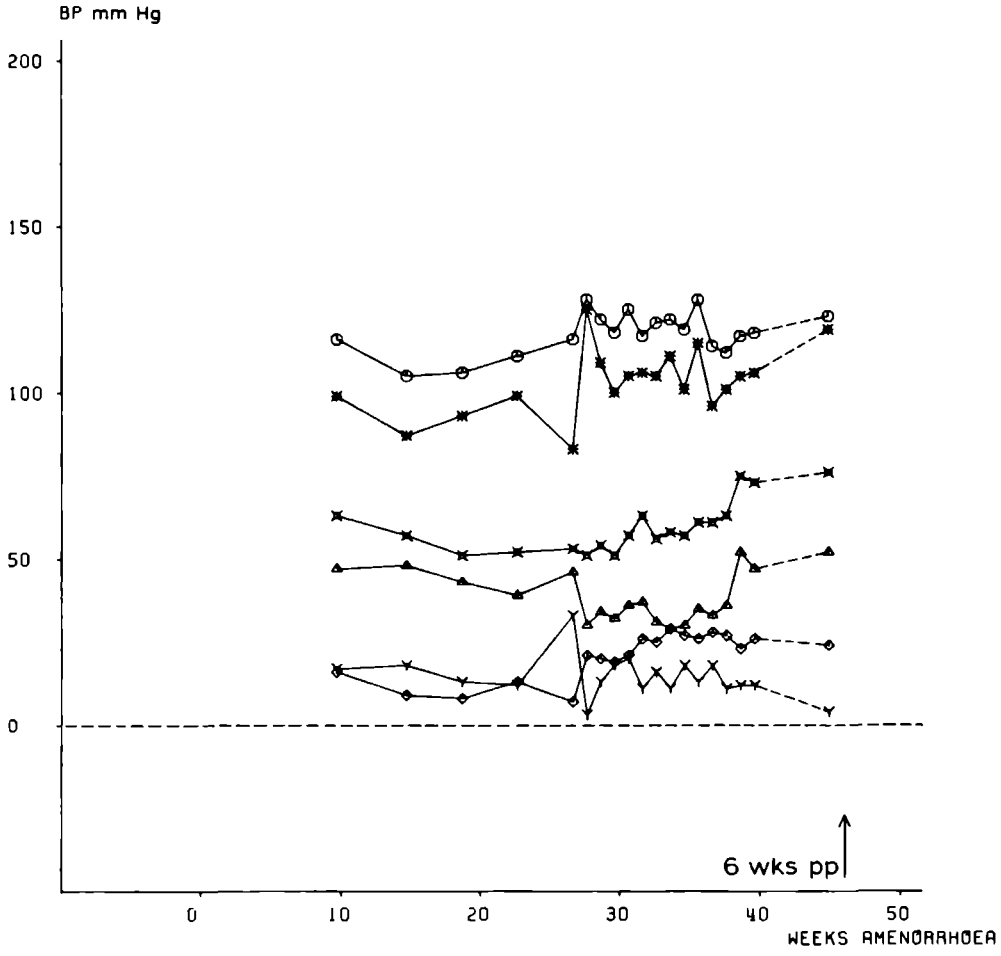



Fig. 9.6 HJ 051152

Secondary infertility. One abortion, parity 0. No pre-existing hypertension, no hypertension during pregnancy, no dysmaturity.

$\overline{\Delta D} > \overline{\Delta S}$ (i.e. $\overline{\Delta P} < 0$).

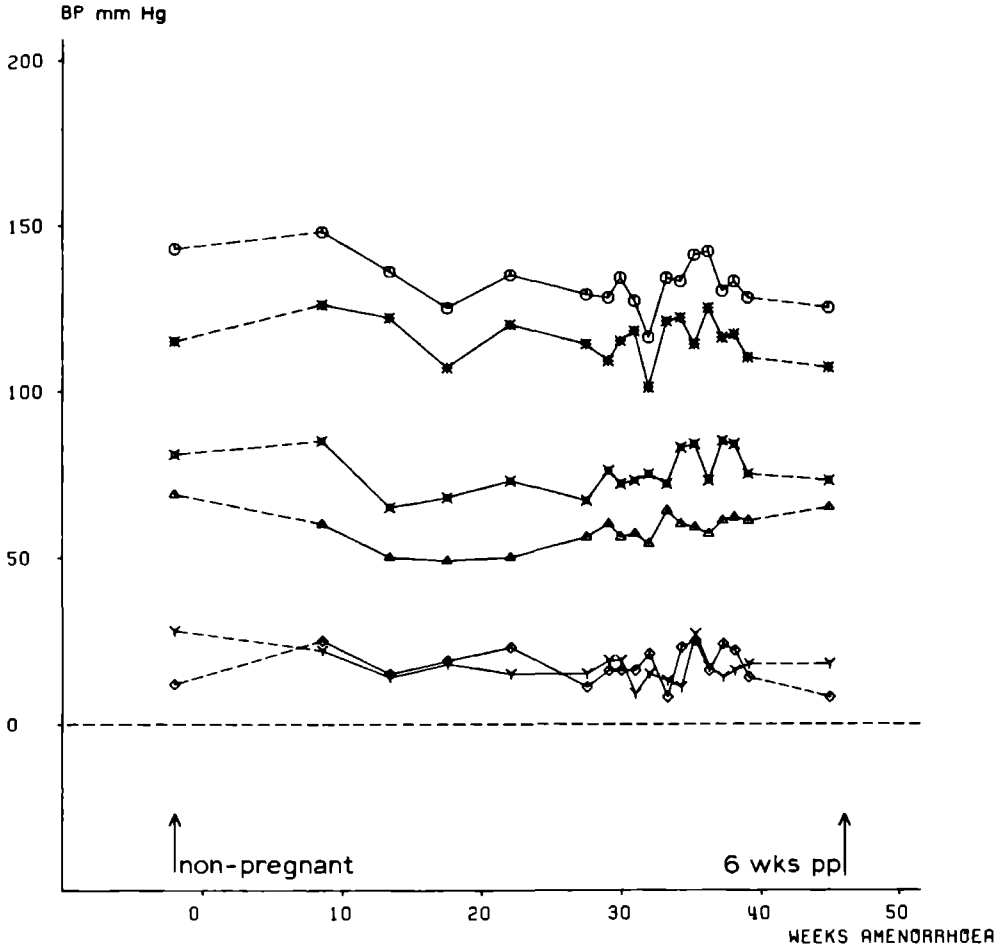



Fig. 9.7 SH 220348

Glomerulonephritis. Pre-eclampsia, parity 1. Pre-existing hypertension, hypertension during pregnancy, no dysmaturity.

$\overline{\Delta D} > \overline{\Delta S}$ (i.e. $\overline{\Delta P} < 0$).

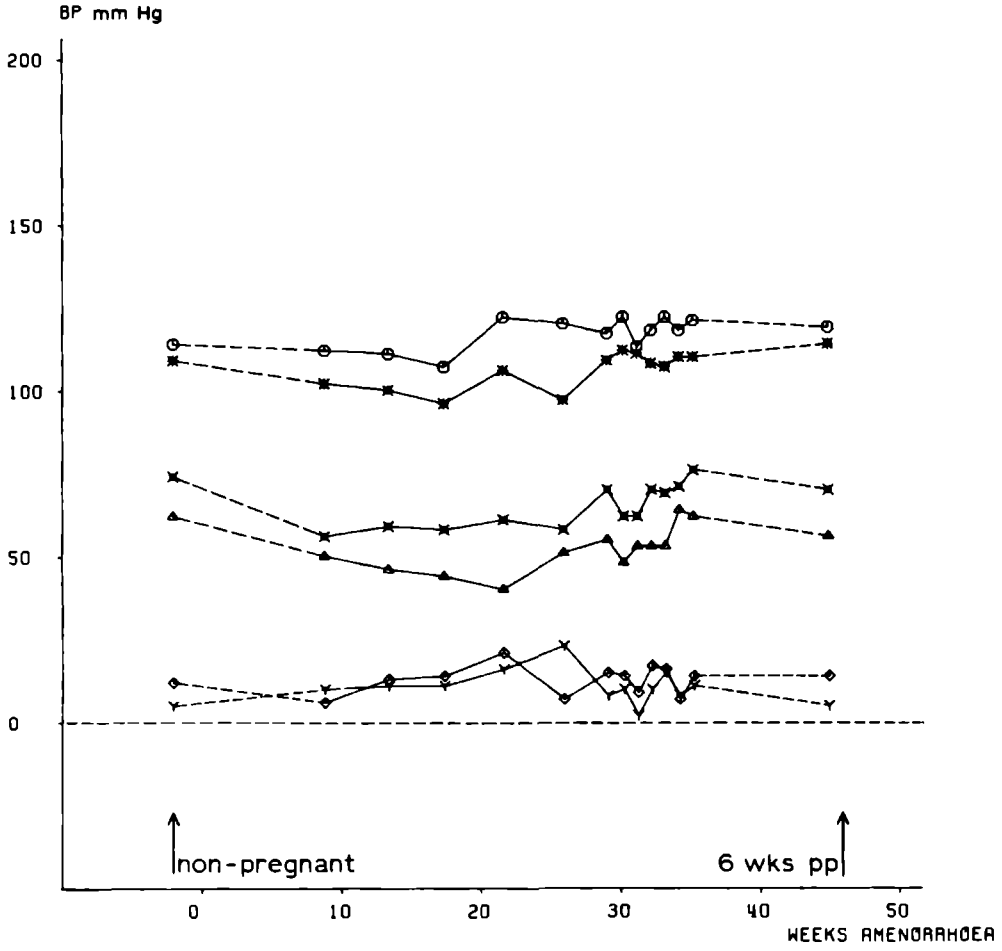



Fig. 9.8 BJ 171154

Intrauterine foetal death, parity 1. Pre-existing hypertension, no hypertension during pregnancy, prematurity and dysmaturity, placental abruption.

$\overline{\Delta D} > \overline{\Delta S}$ (i.e. $\overline{\Delta P} < 0$).

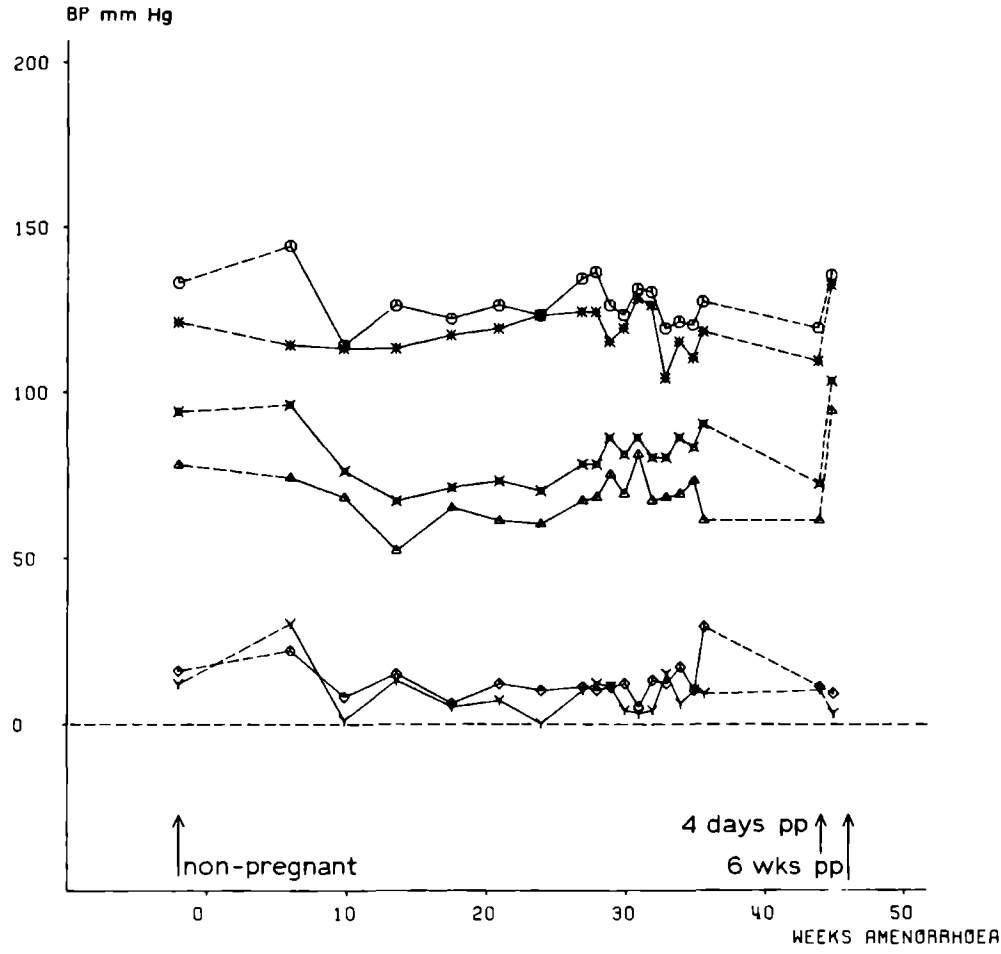
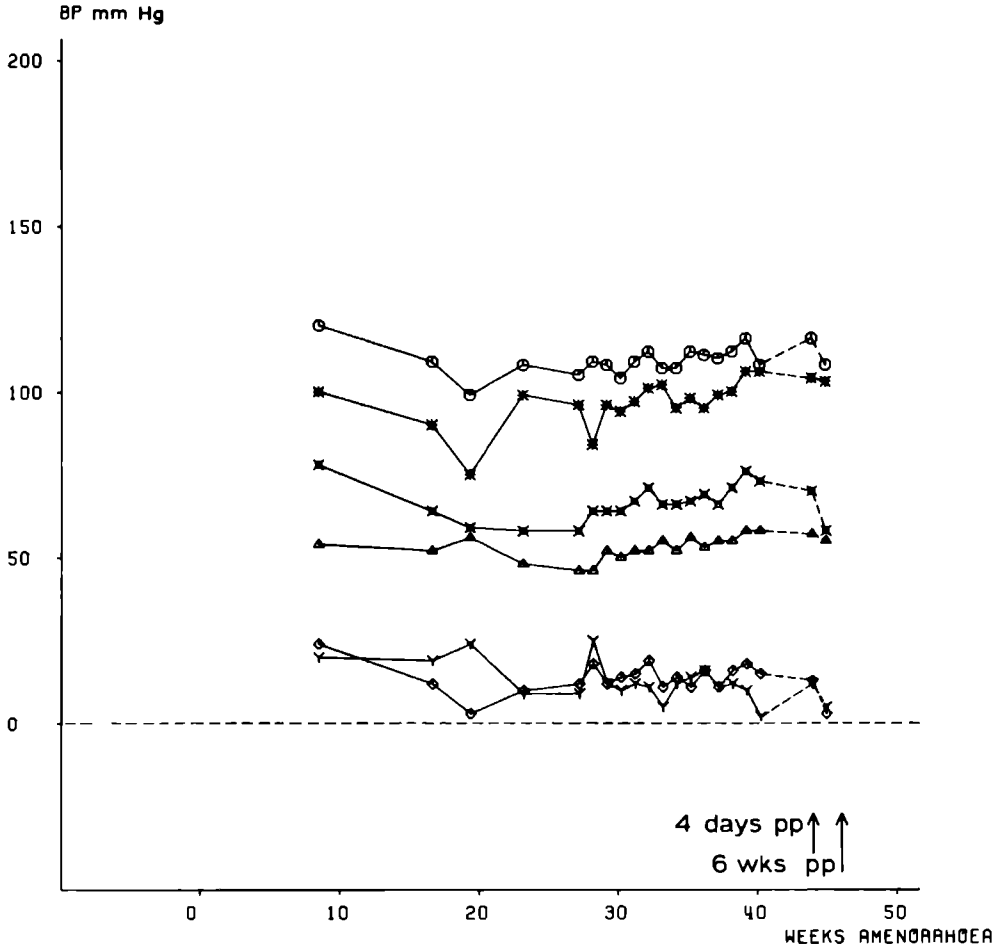



Fig. 9.9 ML 050248

Three abortions, one intrauterine foetal death, parity 2. Pre-existing hypertension, hypertension during pregnancy (α-methyl dopa t.i.d. 250 mg), hypertensive crises, prematurity, no dysmaturity.

$\overline{\Delta D} > \overline{\Delta S}$ (i.e. $\overline{\Delta P} < 0$).




Blood pressures and postural BP differences by ultrasound method

| | |
|---|---|
| SBP supine | DBP supine |
| SBP left lateral | DBP left lateral |
| ΔS | ΔD |

Fig. 9.10 BB 120741

Parity 1. No pre-existing hypertension, hypertension during pregnancy, no dysmaturity.

$\overline{\Delta D} > \overline{\Delta S}$ (i.e. $\overline{\Delta P} < 0$).

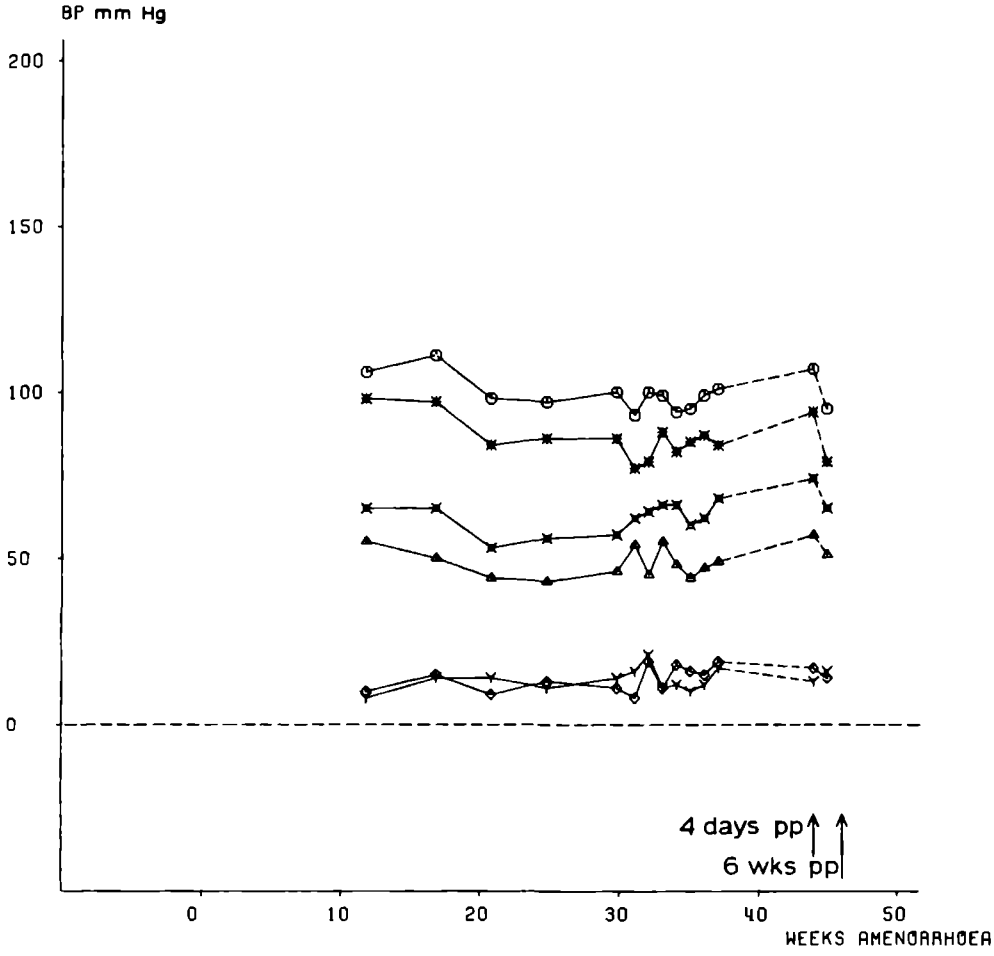



Fig. 9.11 PA 050449

Secondary infertility. Parity 1. No pre-existing hypertension, no hypertension during pregnancy, no dysmaturity.

$\overline{\Delta D} > \overline{\Delta S}$ (i.e. $\overline{\Delta P} < 0$).

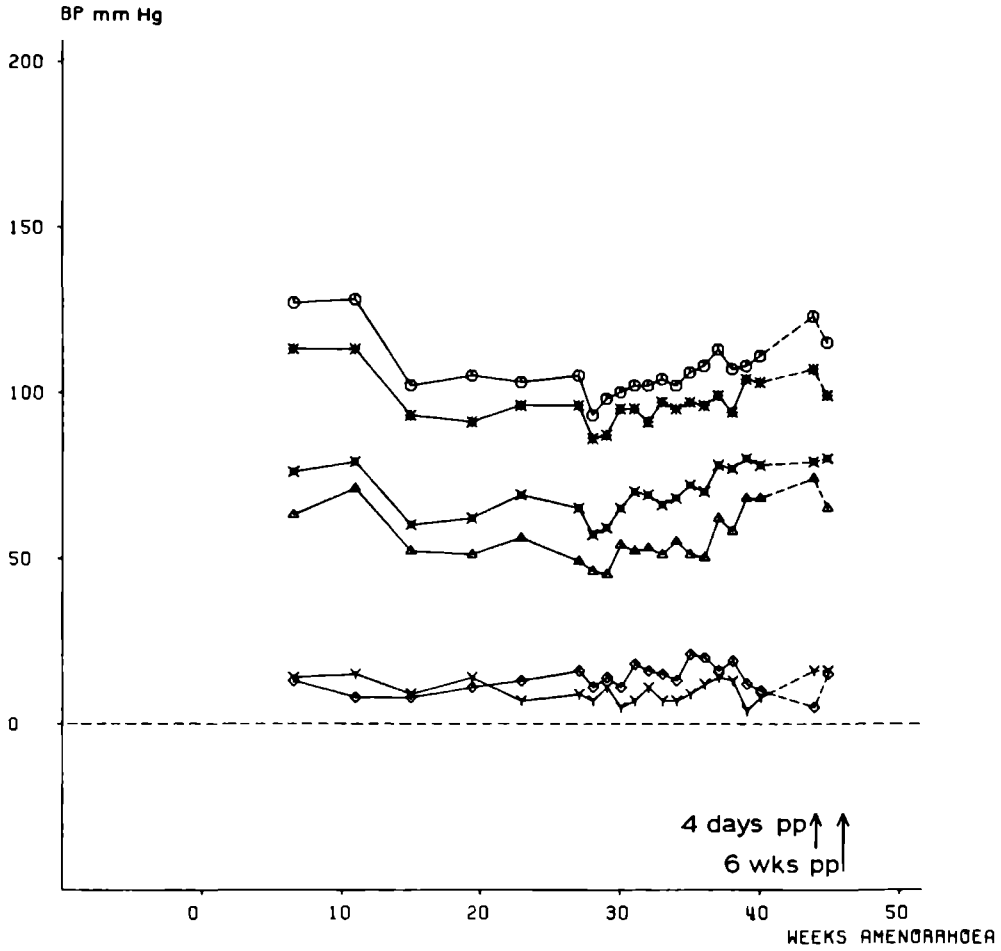



Fig. 9.12 KD 140454

Immature delivery, parity 1. Pre-existing hypertension, hypertension during pregnancy, no dysmaturity, insulin.

$\overline{\Delta D} > \overline{\Delta S}$ (i.e. $\overline{\Delta P} < 0$).

The differences in blood pressure were studied between the supine and left lateral positions in pregnant subjects.
Cross-sectional studies were performed in 125 nulliparous pregnant women after the 28th week of pregnancy and 42 non-pregnant control subjects.
Longitudinal studies were done throughout and after pregnancy in six pregnant nulliparae and six pregnant multiparous women.
The blood pressure measurements were performed under standardized conditions (basal readings) with an automated ultrasound device.

The results of our studies can be summarized as follows:

- Hydrostatic pressure difference plays an important role in determining the blood pressure differences between the supine and left lateral positions. The measured blood pressures, therefore, are lower in the left lateral than in the supine position;
- The magnitude of duplicate errors in postural blood pressure differences, observed in this study, suggests a great caution should be exercised in interpreting such differences, particularly in relation to a fixed criterion of abnormality. The correlation between initial value and postural blood pressure difference is mainly due to the relatively large measurement error. Thus, there was no correlation between the basal systolic and diastolic blood pressures and the postural blood pressure difference;
- Neither hypertension nor pregnancy alone gives an enhanced postural difference in blood pressure;
- Hypertension in pregnancy is associated with a significantly larger positional change in diastolic blood pressure than in systolic blood pressure. The factor responsible for this phenomenon may be the decrease in effective blood volume in the supine position, provoking a somewhat exaggerated vaso-

constrictor response in the hypertensive patients (increased ΔD) and leading also to a reduction in cardiac stroke volume (smaller ΔS than ΔD);

- Neither the postural differences in diastolic blood pressure (ΔD) nor in pulse pressure (ΔP) show a correlation with the incidence of growth retardation and birth weight percentile. However, the postural differences in systolic blood pressure (ΔS) and also in mean arterial blood pressure (ΔM) show a weak but significant correlation with birth weight percentile. The origin of this correlation is not clear, but it may reflect differing degrees of vena caval compression according to foetal (and thus uterine) size;
- Proteinuria did not affect the incidence of growth retardation in this study, most probably because the majority of proteinuric subjects had very mild proteinuria;
- Serial measurements of the postural blood pressure differences during pregnancy in 12 gravidae showed a wide range of values in all subjects, with often sizeable variations in either direction between successive measurements. These measurements did not seem to be predictive of the development of hypertension later in pregnancy, or of dysmaturity, in the individual subjects.

Het bloeddrukverschil tussen rug- en linker zijligging bij patiënten werd bestudeerd in een transversale studie van 125 zwangere nulliparae na de 28e week van de zwangerschap en 42 niet-zwangere contrôle-personen. Longitudinale studies gedurende de zwangerschap en na de zwangerschap werden verricht in 6 nulliparae en 6 multiparae. De bloeddrukmetingen werden verricht onder gestandaardiseerde condities (basale metingen) met behulp van een automatisch registrerend bloeddrukapparaat, gebaseerd op het ultrageluidsprincipe.

Het resultaat van deze studie kan worden samengevat als volgt:

- Het hydrostatische bloeddrukverschil speelde een belangrijke rol bij het bepalen van het bloeddrukverschil tussen rug- en linker zijligging. De gemeten bloeddrukken waren lager in de linker zijligging dan in de rugligging;
- De grootte van de meetfouten, gevonden bij de bepaling van het bloeddrukverschil, maant tot zeer grote voorzichtigheid om zulke verschillen te interpreteren, vooral als het patiënten betreft met een definitie van hypertensie. De correlatie tussen de beginwaarde van de bloeddruk en het gevonden bloeddrukverschil in de twee houdingen werd veroorzaakt door de relatief grote meetfouten. Er was dus geen echte correlatie tussen de basale systolische en diastolische bloeddruk en de bloeddrukverschillen;
- Hypertensie noch zwangerschap alléén vergrootte het bloeddrukverschil tussen de twee houdingen;
- Hypertensie in de zwangerschap ging gepaard met een signficant groter diastolisch dan systolisch bloeddrukverschil. De verantwoordelijke factor voor dit verschijnsel is misschien het verminderd circulerende bloedvolume in rugligging, welke een sterkere vasoconstrictie in hypertensieve zwangeren uitlokt

(grotere ΔD) en tevens aanleiding geeft tot een verminderd slagvolume (ΔS kleiner dan ΔD);

- De bloeddrukverschillen tussen de twee houdingen van zowel de diastolische bloeddruk als van de polsdruk waren niet gecorreleerd met het voorkomen van groeivertraging of de percentielen van het geboortegewicht. Evenwel, de bloeddrukverschillen van de systolische bloeddruk (ΔS) en ook van de gemiddelde arteriële bloeddruk (ΔM) vertoonden een zwakke, maar significante correlatie met de percentielen van het geboortegewicht. De reden voor deze correlatie was niet duidelijk, maar mogelijkerwijs heeft de grootte van de foetus en dus van de uterus invloed op de graad van compressie van de vena cava inferior;
- Proteïnuria vertoonde géén invloed op het vóórkomen van groeivertraging, meest waarschijnlijk omdat de meeste patiënten een zeer milde proteïnuria hadden;
- Longitudinale metingen van de bloeddrukverschillen gedurende de zwangerschap in 12 patiënten gaven een grote spreiding van waarden te zien bij alle patiënten, zowel boven als onder het gemiddelde bloeddrukverschil. Deze metingen lijken dus geen voorspellende waarde te hebben wat betreft het ontstaan van hypertensie laat in de zwangerschap of van het optreden van dysmaturiteit in individuele patiënten.

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Stellingen behorend bij het proefschrift

*"Postural Blood Pressure Differences in Pregnancy"*

Nijmegen, 7 juni 1979 P.W.J. van Dongen

1. De voorkeurshoudıng voor het bepalen van de bloeddruk ıs de rugligging, aangezıen het hydrostatısch drukverschıl tussen het hart en de plaats van bloeddrukmetıng gelıjk te stellen ıs aan nul.

*Dit proefschrift*

2. Iedere bloeddrukmetıng volgens Rıva-Rocci-Korotkow behoort vergezeld te gaan met de vermeldıng ın welke houdıng en bıj welke Korotkow-tonen gemeten ıs.

*Dit proefschrift*

3. Een pıjnstıllend medıcament helpt het meest als de pıjn hevıg ıs.

4. Men moet denken aan het gevaar van "Berkson's fallacy", wanneer de frequentıes van het vóórkomen van het samengaan van verschıjnselen bıj zıekenhuıspatiënten worden vergeleken.

*Berkson,J.(1946).Biomet.Bull.,2,47.*

5. Bıj de analyse van een casus van moedersterfte moet onderscheıd gemaakt worden tussen de "underlyıng cause", d.w.z. dié zıekteverschıjnselen, dıe vanaf het begın van de zıekte tot de dood hebben geleıd, en de "mode of death", d.w.z. de oorzaak, dıe dırect tot de dood heeft geleıd. Het belang van dıt onderscheıd lıgt ın het feıt, dat bıj nauwkeurıge analyse vaak blıjkt dat ın het merendeel van de gevallen gesproken kan worden van vermıjdbare oorzaken.

*Bout,J.(1971). Proefschrift, Amsterdam.*

*Van Dongen et al.(1979). Europ.J. Obstet.Gynec.Reprod.Biol.,vol 9.*

6. Bij het onderzoek van mannen met primaire steriliteit ten gevolge van volledige asthenozoöspermie behoort het uitsluiten van dextrocardie tot de routineprocedure.

*Eliasson et al.(1977). New.Eng.J. Med.,297,1.*

7. Bij het stellen van een indicatie voor amniografie dient het risico van het optreden van schildklierfunctiestoornissen bij het kind in de overwegingen betrokken te worden.

*Rodesch et al.(1976). Am.J.Obstet. Gynecol.,126,723.*

8. De urine, verkregen direct na een insult van een zwangere vrouw, behoort in een gouden schaaltje naar het laboratorium te worden gebracht.

9. De prioriteiten van de gezondheidszorg in ontwikkelingslanden zijn gericht op de instandhouding van de soort, terwijl in de geïndustrialiseerde landen deze prioriteiten zijn gericht op de instandhouding van het individu.

10. Als de mens zo egoïstisch is als wij gewoonlijk aannemen, dan zou de mensheid al lang niet meer bestaan.

11. De theorie, dat de migratie van de Bantu's voornamelijk plaats vond vanuit Shaba, wordt ondersteund door linguïstische argumenten, archeologische vondsten en de verspreiding van de sickle cell trait.

12. Het leven bestaat al vóór de conceptie.