HEMODYNAMIC STUDIES IN PREECLAMPSIA: IMPLICATIONS FOR MANAGEMENT

HEMODYNAMISCH ONDERZOEK BIJ PATIENTEN MET PREËCLAMPSIE: IMPLICATIES VOOR BEHANDELING

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To the memory of my father

to my mother

CONTENTS

Chapter 1

GENERAL INTRODUCTION

Preeclampsia is a condition unique to pregnancy, characterized by hypertension and proteinuria. Nulliparous pregnancies and those affected by preexisting hypertension, diabetes and renal disease are at increased risk. Preeclampsia may develop during pregnancy, labor or in the early puerperium, and it occurs in about 5 percent of all pregnancies[228]. It is a complex clinical syndrome potentially involving all maternal organ systems, with hypertension representing but one manifestation. When generalized convulsions are present, the condition is referred to as eclampsia.

Hypertensive disorders, including preeclampsia, are among the most common complications of pregnancy, and they constitute a major cause of maternal, fetal and neonatal mortality and morbidity worldwide[228]. For the past 10 years hypertensive disorders were the major cause of maternal mortality in England and Wales, and 56 percent of deaths associated with hypertensive disorders of pregnancy were attributed to eclampsia[52]. Douglas and Redman[58] reported a 1.8 percent mortality rate and a 34 percent rate of complications in 383 women with eclampsia treated in the United Kingdom in 1992. Of the 35 maternal deaths registered in the Netherlands in the period 1988-1992, 10 were directly related to eclampsia[51]. With an estimated 100 cases of eclampsia per year in the Netherlands, a Dutch woman with eclampsia has a risk of about 2 percent to die. The most frequent cause of death in eclampsia is cerebral bleeding, followed by respiratory problems.

The perinatal morbidity and mortality related to preeclampsia-eclampsia are not so easy to quantify. A Swedish survey showed a perinatal mortality of 74 percent among infants of eclamptic mothers born after less than 34 weeks' gestation, while it was only 1.8 percent in deliveries after 34 weeks[148]. Preeclampsia accounts for 5.5 to 13 percent of all preterm births in the United States[169]. Derham et al.[53] showed that the duration of pregnancy at delivery was the primary prognostic factor for neonatal outcome in cases of severe early preeclampsia.

Hypertension, the characteristic sign of preeclampsia, demonstrates a disturbance

in the relationship of cardiac output and systemic vascular resistance, the two factors determining the pressure in the systemic circulation[124]. In the healthy pregnant woman impressive hemodynamic changes occur, which have been extensively reviewed[50,59,230]. Already at a gestational age of 6 weeks blood pressure falls, and rises again to nonpregnant levels in the course of the third trimester[129,205]. The maternal heart rate increases in the early weeks of gestation, followed by a rise in stroke volume[60,93] and resulting in an increase in cardiac output of about 40 percent. This hemodynamic adaptation to pregnancy may be triggered by a primary fall in vascular tone, followed by a compensatory increase in heart rate and activation of volume-restoring mechanisms[60]. The increase in cardiac output reaches a plateau by about 24 weeks and cardiac output remains at approximately the same level until term[60,93], although some studies have found a small decrease after 34 weeks, due to a fall in stroke volume[64,146,189], and others a continuing rise until term[128]. The fall in systemic vascular resistance reaches a nadir at about 25 weeks[7,60], with a progressive rise toward term[59,115], although in the study of Mabie et al.[128] vascular resistance fell consistently until term. Plasma volume increases as early as the sixth week of gestation, and appears to reach a plateau by 30 to 34 weeks, when it exceeds the nonpregnant value by about 40 percent[50,230]. Thereafter it remains at the same level until term, although some studies have reported a small decrease during the last weeks of pregnancy[23,96,123].

Published data on maternal hemodynamics in preeclamptic patients are conflicting and vary from a high-output, low-resistance to a low-output, high-resistance state[64,126,205,230]. The observed hemodynamic variability is usually attributed to a variable pathophysiological expression of the pregnancy-induced hypertensive disorder[33,64,170], but many other factors such as: differences in definition and severity of the disease; unreliable methods to determine hemodynamics; the presence or absence of different treatments; the presence or absence of labor; and small numbers of patients studied; may have affected the results of hemodynamic studies.

Results of hemodynamic studies in preeclamptic patients can only be compared if similar definitions of preeclampsia are used. Unfortunately, almost every investigator in the field of preeclampsia uses a different definition: hypertension and proteinuria; hypertension and/or proteinuria and/or edema; hypertension and/or proteinuria, and/or edema, and/or increased uric acid, and/or trombocytopenia, and/or visual disturbances,

and/or persistent headache, and/or epigastric pain, and/or oliguria; and a host of other definitions[229]. The definitions of pregnancy-induced hypertension and preeclampsia adopted by the International Society for the Study of Hypertension in Pregnancy (ISSHP) in 1988 are simple and applicable to patient populations all over the world[46] (Table 1.1).

Table 1.1. *Summary of the definitions and classification of hypertensive disorders in pregnancy, as recommended by the International Society for the Study of Hypertension in Pregnancy. Modified from Davey & MacGillivray 1988*[46]

DEFINITIONS		
Hypertension	1.	One indirect measurement of diastolic blood pressure (Korotkoff 4) of 110 mm Hg or more, or
	2.	Two consecutive indirect measurements of DBP of 90 mm Hg or more, 4 hours or more apart.
Proteinuria	1.	Total protein excretion of 300 mg or more per 24 hours.
	2.	Two random clean-catch or catheter urine samples collected 4 hours or more apart, with (a) $^{++}$ (1 g/l) or more on reagent strip if SG is more than 1030 or (b) $^{+}$ (0.3 g/l) or more if SG is less than 1030.
CLASSIFICATION		
Pregnancy-induced hypertension (PIH)	Hypertension developing after 20 weeks of pregnancy in a previously normotensive nonproteinuric woman.	
Preeclampsia (proteinuric PIH)	Hypertension in combination with proteinuria developing after 20 weeks' gestation in a previously normotensive non-proteinuric woman.	
Chronic hypertension or chronic renal disease	Hypertension and/or proteinuria in pregnancy in a woman with chronic hypertension or chronic renal disease diagnosed before or during, or persisting after pregnancy.	
Chronic hypertension with superimposed preeclampsia	Proteinuria developing for the first time during pregnancy in a woman with chronic hypertension.	
Unclassified hypertension and/or proteinuria	Hypertension and/or proteinuria found at first antenatal examination after 20 weeks' gestation. May be classified after delivery.	
Eclampsia	The occurrence of generalized convulsions during pregnancy, labor, or within 7 days of delivery, and not caused by epilepsy or other convulsive disorders.	

Until about 1990 it was generally recommended[46,168,243] to use phase 4 of the Korotkoff sounds (the point at which the sounds becomes muffled) in indirect measurement of blood pressure in obstetric patients to define diastolic pressure, but recent publications[100,154], especially from the United States, recommend the use of phase 5, as in nonobstetric practice, because it would more closely represent true intra-arterial diastolic blood pressure. However, a recent study[75] showed that the difference between

phase 4 and phase 5 is often very small, in particular in preeclamptic women, so that it is unlikely that a recommendation to use one rather than the other would make a significant difference.

Blood pressure is recorded most accurately by the invasive intra-arterial method. Although this approach is much too invasive and impractical for routine measurement of systemic arterial pressure, it has obvious advantages in the management of pregnant patients with a severe hypertensive disorder. Intra-arterial monitoring of systemic blood pressure immediately indicates changes in perfusion pressure that may require instantaneous therapeutic action, and in addition it allows sampling for assessment of blood gases and acid-base status, which is often required in patients with severe preeclampsia or eclampsia.

Assessment of cardiac output is even more complicated than that of systemic blood pressure. There is no direct method of determining cardiac output in man. Many indirect invasive (direct Fick, dye dilution, thermodilution,) as well as noninvasive methods (earpiece densitometry, electrical impedance cardiography, echocardiography and Doppler ultrasound procedures) have been used in normotensive and preeclamptic pregnant patients[56,109,124,230]. The direct Fick method, based on oxygen consumption divided by the arteriovenous oxygen difference over the lungs as determined by right-heart catheterization and sampling of pulmonary arterial blood, is still regarded as the gold standard for measuring cardiac output in man[67], but it has been replaced by thermodilution using the Swan-Ganz pulmonary artery catheter in the clinical intensive care of severely ill patients[56,109,124], including obstetric patients[230]. An additional advantage of the Swan-Ganz catheter is that it also allows assessment of central venous and pulmonary intravascular pressures, which is essential in the management of patients with preeclampsia to prevent pulmonary edema[4,27,233]. For these reasons as well as for reasons of accuracy and precision[114], central hemodynamic monitoring using the Swan-Ganz thermodilution catheter is to be preferred over noninvasive methods such as echocardiography combined with continuous or pulsed wave Doppler, or dye-dilution methods using earpiece densitometry, in the intensive care management of pregnant or postpartum patients with severe preeclampsia and eclampsia.

The proper interpretation of central hemodynamic data established in preeclamptic patients with the use of the Swan-Ganz catheter is hampered by a lack of

physiological reference values obtained in healthy, normotensive pregnant women by means of the same invasive method. As yet there are only two reports on Swan-Ganz thermodilution measurements of cardiac output in normotensive pregnant women, one study including seven parous[233] and one study 10 nulliparous healthy pregnant women[29] in the last trimester of uncomplicated pregnancy. Severe preeclampsia necessitating invasive hemodynamic monitoring usually occurs in the late second or early third trimester, and central hemodynamic data obtained in that period of uncomplicated pregnancy seem necessary to allow proper interpretation of the hemodynamic profiles in patients with severe preeclampsia.

Close examination of hemodynamic data obtained with the use of the Swan-Ganz thermodilution catheter in preeclamptic patients[14,33,126,170,176] reveals that almost all studies were carried out during or shortly after pharmacologic antihypertensive and/or anticonvulsive treatment, which may have had a marked influence on the results. In addition, other variables that may modulate the hemodynamic state, such as parity; labor[186,222]; underlying cardiac, renal, or hypertensive disease; and the severity of the hypertensive disorder were not taken into account in the majority of published studies. To determine the pathophysiological hemodynamic profile in patients with preeclampsia, measurements should be performed in well-defined, untreated preeclamptic patients without known preexisting vascular disease, who are not in labor.

As yet the only causal treatment of preeclampsia consists of delivery of fetus and placenta. Such treatment may benefit the mother but is often not in the interest of the second patient, the fetus, in particular remote from term. Although delaying delivery may be expected to reduce neonatal morbidity and mortality[120,162,207], it could also be associated with an increased risk of maternal complications[162,191]. At present most obstetricians will try to postpone delivery in patients with mild preeclampsia and a gestational age of approximately 32 weeks or less, but temporizing management in patients with severe preeclampsia or eclampsia, in particular when complicated by the HELLP syndrome, is disputed[191]. In most centers the HELLP syndrome is considered an indication for immediate delivery, irrespective of gestational age[191,209,236,242]. If it is decided to prolong pregnancy in patients with severe preeclampsia, temporizing treatment based on correction of the disturbed maternal circulation seems a logical approach. Proper control of maternal blood pressure must be considered an essential

part of temporizing management in order to protect the mother from the risks of cerebral hemorrhage and generalized arteriolar injury. The vasodilator (di)hydralazine is the most frequently used antihypertensive agent in the treatment of severe hypertension in patients with severe preeclampsia all over the world[10,43,111]. However, severe hypotension and even hypovolemic shock have been reported to occur with this drug[111] in preeclamptic women, who often have a contracted circulating volume[233]. Maternal hypotension may cause a reduction in uteroplacental blood flow leading to fetal distress[54,112]. If the contracted plasma volume in preeclamptic women is accepted to be responsible, at least in part, for the severe hypotensive effects of (di)hydralazine, these adverse effects may be prevented by correcting circulating volume by plasma volume expansion. Even plasma volume expansion alone may have an antihypertensive effect in preeclamptic patients[74]. As yet limited data on the central hemodynamic effects of (di)hydralazine, with or without plasma volume expansion, in preeclamptic patients are available[12] and further assessment seems worthwhile. Attempts to delay delivery in patients with early severe preeclampsia by means of correction of the disturbed maternal hemodynamic state using pharmacologic vasodilatation combined with plasma volume expansion under central hemodynamic monitoring have been reported[91,233]. However, the number of patients involved is far too small to allow assessment of the beneficial or adverse effects of such treatment on course and outcome of preeclamptic pregnancy.

(Di)hydralazine is an old and well-known antihypertensive drug with a firmly established safety record in pregnancy, but newer antihypertensive agents are advocated for use in the management of preeclampsia[43,55,111]. One of those drugs is nifedipine, a calcium channel blocking agent with a vasodilator effect[212]. It is potent and fast acting, also when administered orally, and for that reason it is recommended for use in hypertensive emergencies[66]. If the results with nifedipine reported in nonpregnant hypertensive patients also hold for pregnant women with severe preeclampsia, nifedipine could be a useful alternative for the treatment of hypertensive emergencies in these patients. However, the central hemodynamic effects of nifedipine in preeclamptic patients are unknown.

Based on the considerations presented above, the objectives of this thesis are:

1. to determine central hemodynamics in healthy, normotensive pregnant women in the second and early third trimester. (Chapter 3).

2. to assess baseline central hemodynamics in untreated and treated preeclamptic patients in comparison with data obtained in normotensive pregnant women. (Chapter 4).
3. to evaluate the effects of pharmacologic vasodilatation and plasma volume expansion on central hemodynamics in preeclamptic patients. (Chapter 5).
4. to analyze the course and outcome of pregnancy in patients with severe preeclampsia remote from term, with or without the HELLP syndrome, managed with temporizing hemodynamic treatment under central hemodynamic monitoring. (Chapters 6,7).
5. to compare the obstetric and perinatal results of hemodynamic and conservative temporizing management of patients with severe preeclampsia. (Chapter 8).
6. to study and compare the hemodynamic effects of oral nifedipine and intravenous dihydralazine in patients with severe preeclampsia. (Chapter 9).

The chapters on the various studies reported in the thesis are preceded by a review of the methods of invasive systemic and pulmonary hemodynamic monitoring that were used (Chapter 2) and followed by a general discussion of the results related to the objectives listed above. (Chapter 10).

Chapter 2

METHODS OF INVASIVE SYSTEMIC AND PULMONARY HEMODYNAMIC MONITORING

I was watching the sailboats going by one September afternoon on Santa Monica bay, and I thought, "Why not put a sail on the end of a catheter!" H.J.C.Swan, 1978.

In this chapter the methods of invasive monitoring of the systemic and pulmonary circulations, used in the clinical experimental studies and in the management of patients with severe preeclampsia reported in this thesis, will be presented and aspects relevant to the following chapters will be discussed.

2.1. Monitoring of systemic arterial blood pressures

Arterial catheterization has been used in clinical medicine since the 1950s. Initially, it was employed primarily for diagnostic angiography, but in the management of severely ill patients over the past three decades the use of indwelling arterial catheters has become common practice[28].

The two main indications for arterial catheterization are a need for continuous arterial pressure monitoring, and for multiple blood sampling. The direct intra-arterial technique is the most accurate method of continuous measurement of systemic blood pressures[105,124]. It immediately indicates changes in systemic perfusion pressure that may require instantaneous therapeutic action in critically ill nonpregnant as well as pregnant patients. In addition, the catheter allows frequent arterial sampling for assessment of blood gases and acid-base status, which is also often required in the management of patients needing intensive care. The usual arterial access sites are the radial, femoral and brachial arteries.

A variety of catheters and cannulation systems are available, including catheter-over-needle systems, which are used primarily for radial artery insertion, and catheter-plus-guidewire devices. The radial artery is frequently used for cannulation. Because of the dual circulation to the hand, the radial arterial approach has a low risk of serious

vascular complications and is the best site in terms of patient comfort[2].

Insertion of the radial artery catheter

For the direct measurement and monitoring of systemic arterial pressures reported in this thesis we cannulated a radial artery. Before cannulation, the modified Allen's test was performed to assess the adequacy of the collateral circulation to the hand[195]. For cannulation we prefer to use the same arm in which the Swan Ganz catheter is going to be inserted. The choice of the arm to be used for insertion of the Swan Ganz catheter is determined by the best accessible vein.

Placement of an arterial line is performed by means of aseptic technique to minimize the risk of infectious complications. Hands are scrubbed and sterile gloves and a cap and mask are worn. The hand is supinated and immobilized; a small rolled towel is placed under the patient's wrist to maintain extension, and the entry site is prepared with an antiseptic agent (povidone-iodine or chlorhexidine). The radial artery is then palpated and a 51 mm, 20 gauche catheter (Quik Cath; Baxter Healthcare Corporation. Edwards critical-care division, Irvine CA 92714-5696 USA), is inserted percutaneously under local analgesia (lidocain-HCl 2%) using the catheter-over-needle technique. The needle is introduced at approximately a 45-degree angle to the skin until blood is obtained; the catheter is advanced slowly over the needle into the vessel, and the needle is withdrawn. The presence of pulsatile blood return from the catheter is confirmed before connecting the transducer and the flush system. The catheter is flushed with heparinized saline (5U/ml; 3ml/hr) using a continuous flush system (Triple line customer kit; Ohmeda B.V., Bilthoven, The Netherlands).

Measurement and recording of arterial pressures

Pressures were measured with appropriate disposable strain-gauge pressure transducers (Triple line customer Kit; Ohmeda B.V., Bilthoven, The Netherlands) with zero reference 8 cm below the second intercostal space. For correct positioning of the transducer a measuring device was constructed, consisting of two rods, each with a level, connected by a hinge that allows pivoting in a horizontal plane (Fig. 2.1.). The centers of the rods are 8 cm apart. The upper rod is put on the sternum at the second intercostal space and, when both levels indicate that the rods are horizontal, the lower

rod indicates the correct position of the transducer at the zero reference point. After each change in position of the patient and before each measurement the position of the transducer is checked and the transducer zeroed.

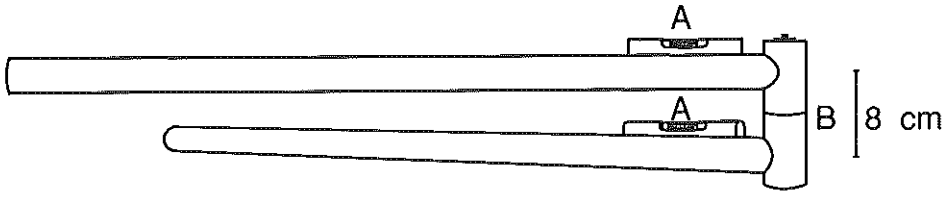


Fig 2.1. *Device consisting of two rods, each with a level (A), connected by a hinge (B) that allows pivoting in a horizontal plane. The distance between the centers of the rods is 8 cm. The device is used to position the pressure transducer at a level of 8 cm below the second intercostal space.*

The systemic arterial pressures in preeclamptic patients reported in this thesis were measured with the patient in supine position after a stabilization period of at least 30 minutes, unless stated otherwise. The blood pressure values were usually read from the monitor (from 1985-1990 model 78354A, Hewlett-Packard, Böblingen, FRG, and since 1990 a Merling monitor, model M1166A, with a pressure module, model M1006A, Hewlett-Packard, Böblingen, FRG), but were also recorded on paper when necessary.

2.2. Monitoring of right atrial and pulmonary blood pressures

For reliable measurement of central venous and pulmonary intravascular pressures invasive procedures cannot be avoided. There is general agreement that the flow-directed balloon-tipped multilumen pulmonary artery catheter developed by Swan et al. in 1970[216] provides the most reliable method of measuring right atrial (central venous), pulmonary arterial and venous pressures. Different models are available, with three, four or five lumina, which allow measurement of pressures in the right heart and the pulmonary vascular system, and through which blood samples can be drawn and fluids injected or infused.

Insertion of the Swan-Ganz catheter

A normal baseline electrocardiogram was obtained from all patients. During the measurements the electrocardiogram was continuously recorded. For the measurements reported in this thesis we used the Paceport (model SP5537H, Ohmeda B.V., Bilthoven, The Netherlands) five lumen Swan-Ganz (SG) catheter shown in Fig 2.2.

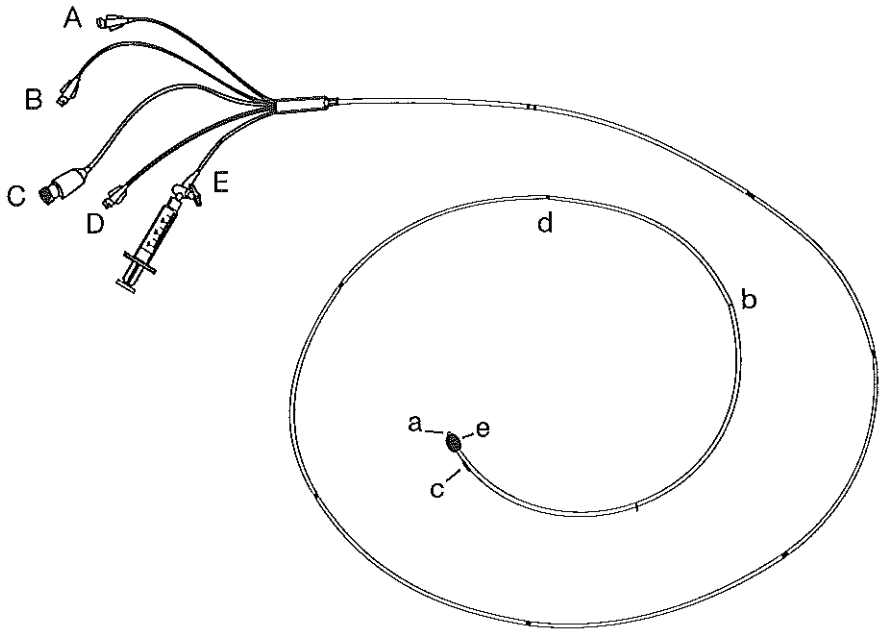


Fig 2.2. *The Paceport five lumen Swan-Ganz catheter.*
A = distal port, opening at a,
B = pace port, opening at b,
C = connection to thermistor cardiac output computer,
c = thermistor,
D = proximal port, opening at d,
E = port for inflation of the balloon at e.

The length of the catheter is 110 cm and the external diameter 7.5 F. The marks on the catheter shaft indicate distances of 10 cm. The five lumina of the catheter consist of a proximal port terminating 30 cm from the tip, allowing measurement of right atrial pressures and injection of chilled fluid for determination of cardiac output; a distal port opening at the tip of the catheter for measurement of pulmonary artery and pulmonary

capillary wedge pressures; a lumen for inflation of the balloon, located 1 mm from the tip; a lumen that contains the electrical leads for the thermistor positioned at the catheter surface, 4 cm proximal to its tip; and finally a lumen that opens 19 cm from the tip and allows the passage of a pacing electrode probe for temporary intracardiac pacing, which we used for additional central venous access.

Using a percutaneous guidewire-sheath procedure (Seldinger technique), the SG catheter is introduced into a large vein and advanced into the right heart under continuous oscilloscopic pressure waveform monitoring. The principle of the Seldinger method is venous puncture with a small needle followed by a wire to secure the position in the vein and provide a path for a vein dilator and an introducer. Routes that can be used are the antecubital, femoral, subclavian and jugular route[45]. We prefer the antecubital route via the basilic vein. The choice of the arm to be used is determined by the best accessible vein.

Under aseptic conditions, as described for arterial cannulation, a catheter-over-needle (Venflon, 45 mm, 17 gauche, Ohmeda, Helsinborg, Sweden) is introduced and, when venous blood returns, the needle is removed and a guidewire is threaded in. Holding the guide wire in place, the cannula is withdrawn from the vessel by pulling it over the guide wire. A small incision is made under local analgesia with 2% lidocaine-HCl to enlarge the puncture site and a vein dilator together with the introducer sheath (Desilet, 8 F., Vygon, Ecouen, France) (Fig. 2.3) is inserted over the wire.

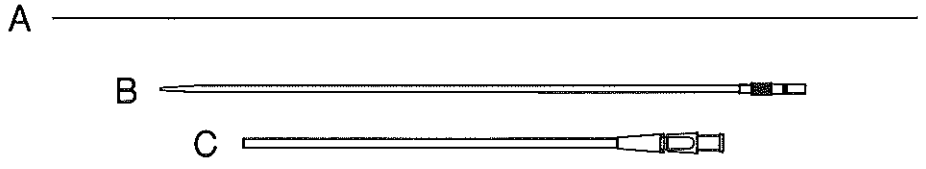


Fig. 2.3. *The introducer sheath (Desilet)*
A = Guide wire
B = Vein dilator
C = Introducer sheath

Next, the guidewire and vein dilator are removed, leaving the introducer sheath in the vessel. Stopcocks are connected to the various ports of the catheter and the lumina are filled with flush solution, consisting of NaCl 0.9% with heparine (5 U/ml). The distal and proximal ports are connected to the pressure transducers. The balloon is inflated with 1.5 ml of air, checked for leaks, and deflated. The Swan-Ganz catheter is inserted through the introducer sheath into the vein and advanced until the tip is located in the right atrium. This requires advancement of approximately 35 to 40 cm from the left antecubital fossa, or 40 to 45 cm from the right antecubital fossa. A right atrial wave form on the monitor with appropriate fluctuations accompanying respiratory changes or cough confirms the correct location (Fig. 2.4A).

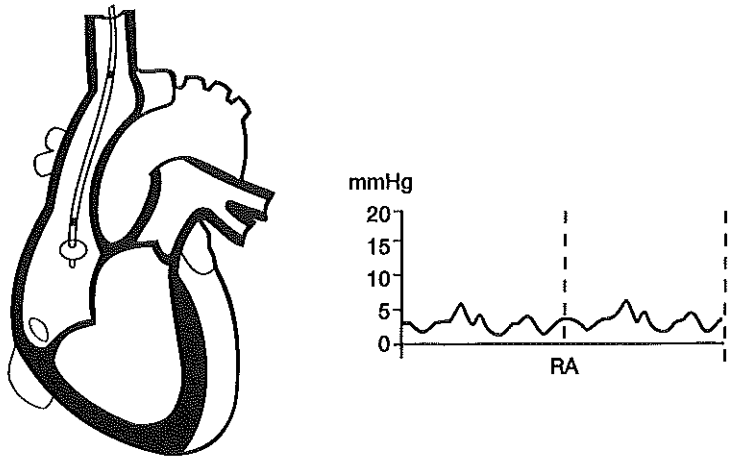


Fig 2.4A *Advancement of the Swan Ganz catheter through the heart with the appropriate hemodynamic waveform.*
RA = Right Atrium. Modified from Hanneman 1991[86]

When the tip has reached the right atrium, the balloon is inflated with 1.5 ml of air. With the balloon inflated, catheter advancement is continued until a right ventricle pressure tracing appears on the monitor (Fig. 2.4B). Passage of the catheter into and through the ventricle is often accompanied with some transient premature ventricular contractions. When the catheter tip reaches the pulmonary artery, the diastolic pressure tracing shows a rise above the right ventricular diastolic pressure (Fig. 2.4C).

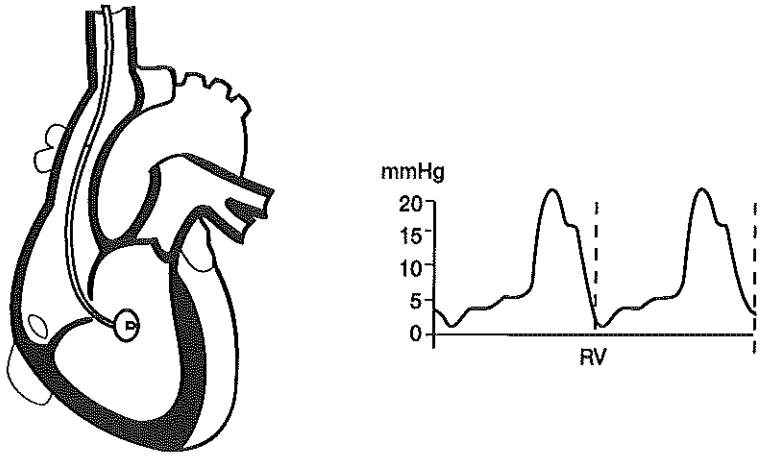


Fig. 2.4B as Fig. 2.4A. RV = Right ventricle

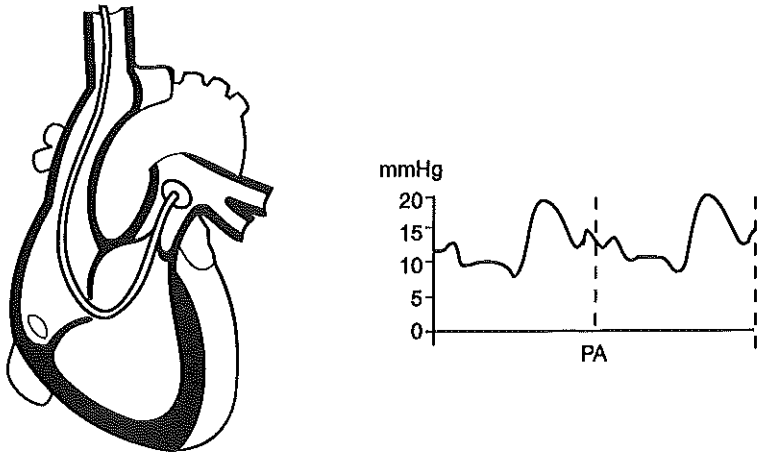


Fig. 2.4C as Fig. 2.4A. PA = Pulmonary artery

Further advancement results in a fall of the pressure; the balloon becomes wedged in one of the small branches of the pulmonary artery, forward blood flow is interrupted, and the tip of the catheter only measures the pressure distal to it, the pulmonary capillary wedge pressure (PCWP) (Fig. 2.4D).

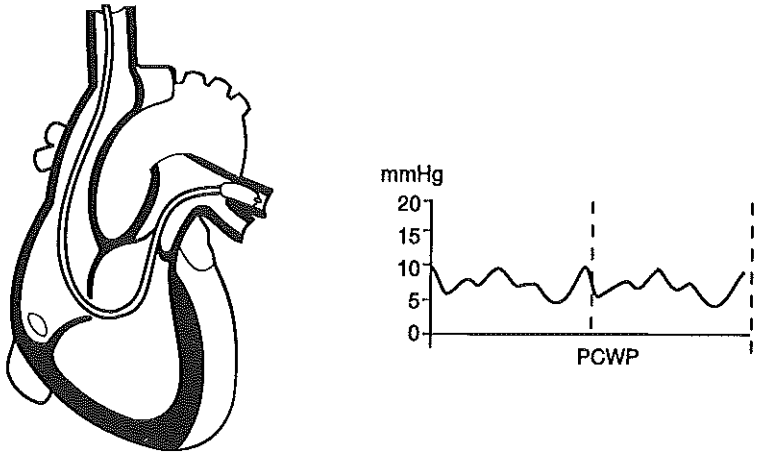


Fig. 2.4D as Fig. 2.4A. PCWP = Pulmonary capillary wedge pressure

After deflation of the balloon a pulmonary artery pressure tracing reappears. In patients with normal heart rate and pulmonary vascular resistance, the diastolic pulmonary pressure is usually within 1 to 3 mm Hg of the PCWP, a relationship that should always be verified to ensure that the distal port is not obstructed, resulting in false high PCWP values. To keep the catheter in its correct position in the pulmonary artery, it is sutured and taped to the skin. A follow-up chest roentgenogram is made to check for catheter position. The proximal and distal lumina of the catheter are continuously flushed with heparinized saline (5 U/ml; 3ml/hr) using a continuous flush system (see 2.1)

Measurement and recording of right atrial and pulmonary blood pressures

For measurement of right atrial and pulmonary intravascular pressures disposable strain-gauge pressure transducers were used with a zero reference 8 cm below the second intercostal space as determined with the measuring device described in Chapter

2.1. After each change in position of the patient and before each measurement the position of the transducer was checked and the transducer zeroed. Right atrial and pulmonary intravascular pressures were obtained, after a stabilization period of at least 30 minutes, at end-expiration, with the patient in supine position, unless stated otherwise.

Pressure values were usually read from the monitor, as described in Chapter 2.1., but were also recorded on paper, when necessary.

2.3. Monitoring of cardiac output

The thermodilution method for measurement of cardiac output was first described by Fegler in 1954[71], who applied the indicator-dilution principle to the use of a known temperature as the indicator. Although the first use of thermodilution for measurement of cardiac output in man was published by Branthwaite et al. in 1968[19], the method did not gain clinical acceptance until the early seventies, when Swan, Ganz and coworkers introduced the flow-directed balloon-tipped and thermal sensitive pulmonary artery catheter[77,216]. A sterile chilled solution is injected via the proximal port into the right atrium, and the resultant change in the temperature of the blood downstream is measured by the thermistor located 4 cm proximal to the catheter tip. A cardiac output microprocessor determines the area under the time-temperature dilution curve, solves the indicator-dilution equation, and calculates flow after appropriate corrections. Although thermodilution and dye-dilution curves are similar, the area under the thermodilution curve can be determined more accurately because of a reduced recirculation effect[67].

The thermodilution measurement of cardiac output correlates closely with both Fick and dye-dilution methods of determining cardiac output, except at low cardiac outputs and in the presence of intracardiac shunts or tricuspid regurgitation[45,153]. The reported standard error of the mean of repeated thermodilution cardiac output measurements when performed in triplicate ranges from 2.0 to 5.0 percent[67,214].

Measurement and recording of cardiac output

Chilled injectate is obtained from a closed system (model 4833747, Baxter Healthcare, Edwards Critical-Care Division, Irvine, USA) utilizing a prechilled bag of

5% glucose solution with its tubing coiled inside a cooling container (Model 93-520 Baxter Healthcare, Edwards, Critical-Care Division, Irvine, USA). A temperature probe is placed between the syringe and the stopcock at the proximal lumen. Ten ml of chilled (5-7°C) 5% glucose solution is rapidly injected into the right atrium via the proximal lumen of the Swan-Ganz catheter. The temperature dilution curve is shown on the monitor for visual inspection, and analyzed by the computer; the calculated value of cardiac output is read from the display. For calculation of cardiac output we used an Edwards Laboratories, Irvine, Calif. computer between 1985 and 1990, and a Merling monitor with cardiac output module Model 1012A after that time. The computer constant must be adjusted for the injectate temperature and the type of catheter used. All measurements were performed at end-expiration with the patient in supine position, unless stated otherwise, in triplicate, and the arithmetic mean was taken as the final value.

To allow comparison between individuals of different size, volumetric cardiac output and calculated systemic and pulmonary vascular resistances were indexed by body surface area (BSA), estimated from the classic Dubois equation with the use of actual height and weight[233].

2.4. Definitions of hemodynamic variables

The following hemodynamic variables were derived from the data obtained by means of the pulmonary artery thermodilution catheter.

EQUATIONS	UNITS
$\text{Cardiac index (CI)} = \frac{\text{cardiac output (CO) (l/min}^{-1})}{\text{body surface area (BSA) (m}^2)}$	$(\text{l.min}^{-1}.\text{m}^{-2})$
$\text{Stroke volume (SV)} = \frac{\text{CO (ml/min}^{-1})}{\text{heart rate (beats.min}^{-1})}$	(ml.beat^{-1})

Stroke volume index (SI)=

$$\frac{\text{SV (ml.beat}^{-1}\text{)}}{\text{BSA (m}^2\text{)}} \quad \text{(ml.beat}^{-1}\text{.m}^{-2}\text{)}$$

Systemic vascular resistance (SVR)=

$$\frac{\text{[Mean arterial pressure (MAP)(mmHg)-right atrial pressure (RAP)(mmHg)] x 80}}{\text{CO (l.min}^{-1}\text{)}} \quad \text{(dyn.s.cm}^{-5}\text{)}$$

Systemic vascular resistance index (SVRI)=

$$\frac{\text{[MAP (mmHg) - RAP (mmHg)] x 80}}{\text{CI (l.min}^{-1}\text{.m}^{-2}\text{)}} \quad \text{(dyn.s.cm}^{-5}\text{.m}^2\text{)}$$

Pulmonary vascular resistance (PVR)=

$$\frac{\text{Mean pulmonary arterial pressure (MPP) (mmHg) - PCWP (mmHg) x 80}}{\text{CO (l/min)}} \quad \text{(dyn.s.cm}^{-5}\text{)}$$

Pulmonary vascular resistance index (PVRI)=

$$\frac{\text{[MPP (mmHg) - PCWP (mmHg)] x 80}}{\text{CI (l.min}^{-1}\text{.m}^{-2}\text{)}} \quad \text{(dyn.s.cm}^{-5}\text{.m}^2\text{)}$$

Left ventricular stroke work index (LVSWI)=
SI (ml.beat^{-1}.m^{-2}) x [MAP (mmHg) - PCWP (mmHg)] x 1332 x 10^{-7} (J.beat^{-1}.m^{-2})

Right ventricular stroke work index (RVSWI)=
SI (ml.beat^{-1}.m^{-2}) x [MPP (mmHg) - RAP (mmHg)] x 1332 x 10^{-7} (J.beat^{-1}.m^{-2})

2.5. Discussion

Although trends in systemic arterial blood pressure can be monitored using a noninvasive, automated Doppler or oscillometric device, such measurements require frequent occlusion of a cuff, which means added discomfort for the severely ill patient. Moreover, these methods may produce grossly erroneous readings[94,95,101,195]. Photoplethysmography is a new noninvasive method that provides continuous recordings

of systolic and diastolic pressures, but peripheral vasoconstriction may result in inaccurate readings[21]. Also the possibility of frequent arterial blood sampling for determination of blood gases and acid-base status offers a clear advantage of the intra-arterial catheter in the management of the severely ill patient. However, arterial catheterization carries certain risks. The most common complications are vessel perforation, bleeding, thrombosis and infections[28,78,159]. Hemorrhagic complications are generally minor, especially with radial artery catheterization, because the radial artery can be compressed easily. Bleeding complications are more common in elderly, obese individuals, in patients with bleeding diathesis, or in those receiving anticoagulants[28]. The risks of infections, bacteremia and sepsis associated with arterial catheters have been reported to reach an incidence of up to 9 percent[8,159,217,219]. The risk of infection increases with the time the catheter remains in place[8,159] and for that reason we always removed the catheters within 72 to 96 hours. To further lower the risk of infectious complications we used a percutaneous approach with strict aseptic insertion techniques, and disposable transducers[28,195]. Catheter-related infections have been reported to result in pseudoaneurysm formation and arterial rupture in rare instances[5,28,217]. A potentially dangerous complication may occur if the connector used in arterial catheterization accidentally becomes loose. Exsanguination may threaten the patient's life if this problem is not quickly detected and dealt with[152]. Inadvertent injection of medication into an arterial catheter is another accident that may cause severe injury[152].

As yet the most reliable method to determine central venous and pulmonary intravascular pressures appears to be via the Swan-Ganz pulmonary artery catheter[109,124]. Although noninvasive methods have been proposed to estimate pulmonary pressures using echocardiography[1,6] or Doppler echocardiography[106,113,142,144,186] the validity of these methods in the clinical setting has to be confirmed[6,113,114].

Case reports describing a variety of complications associated with the use of the Swan Ganz catheter, also in obstetric patients[176], can be found in the literature[185], but the frequency of severe complications appears to be very low, at least in the hands of experienced operators[65,232].

Complications can be divided into three main categories:

1. those associated with venous cannulation; 2. those associated with threading the catheter through the heart into the pulmonary artery; and 3. those associated with the

maintenance of the catheter. Complications of venous cannulation, such as arterial puncture, pneumothorax, hydrothorax, hematothorax and chylothorax, are associated with the subclavian or internal jugular approach[152], and avoided with the use of the antecubital route[196,226]. Bleeding at the antecubital puncture site can easily be stopped, which is an advantage in the patient with hemostatic problems, as in case of the HELLP syndrome. It is said that placement of the Swan-Ganz catheter through an antecubital vein may be associated with a higher rate of thrombosis, and that catheter manipulation is more difficult[226], but our experience with this approach is good, without complications of thrombosis.

The most frequent complication of intracardiac advancement of the catheter is the occurrence of benign, transient arrhythmias[45,226].

Complications associated with maintenance of the catheter are thrombus formation, pulmonary infarction, infection and pulmonary artery rupture[45]. Although thrombus formation may occur with any intravascular catheter, the polivinylchloride material of the pulmonary artery catheter has been shown to be especially thrombogenic[45]. For that reason we use a heparin bonded catheter[92,135,226], and a continuous flush of heparinized saline. Pulmonary infarction may occur as a result of embolization of a thrombus from the catheter, or as a result of catheter migration and prolonged wedging[45,197,226]. To prevent the latter complication, the location of the catheter tip in the proximal pulmonary artery is checked carefully with a chest roentgenogram, the pressure in the distal lumen is continuously monitored, and the catheter is wedged as briefly as possible. To reduce the risk of infectious complications we use meticulous aseptic technique, disposable transducers, and a closed injectate delivery system for cardiac output measurements. Finally, the catheter is always removed within 96, usually 72, hours. To avoid rupture of the pulmonary artery, the most catastrophic complication of pulmonary artery catheterization, the frequency of balloon inflation is kept at a minimum[45]. It is also important to inflate the balloon slowly under continuous monitoring of the pressure tracing on the bedside monitor, and to halt further inflation when a balloon-occluded tracing is obtained[45].

In the past two decades cardiac output measurement by means of the thermodilution technique using the Swan-Ganz catheter has become an integral part of medical and surgical intensive care and, more recently, also in the management of

critically ill obstetric patients, including patients with severe preeclampsia[4,127,232]. The thermodilution method is accurate and reproducible; it allows serial determination of cardiac output over several days; and the pressures in the pulmonary circulation may be determined at the same time[109,124]. Several studies[45,198,214] have shown that volume, injectate temperature, and timing of injection markedly affect the results of thermodilution measurement of cardiac output. The volume of 10 ml and the temperature of 5-7°C used for the injectate in our studies is recommended as yielding sufficient accuracy and precision[153]. Timing of the injection is essential, because the baseline temperature in the pulmonary artery varies with respiration[67,153]. The best thermodilution curve will be obtained during apnea, but this is obviously impractical. We standardized measurement of cardiac output during end-expiration in an attempt to eliminate this source of variability.

Techniques of combined echocardiography and pulsed or continuous wave Doppler ultrasound for noninvasive determination of cardiac output are developing rapidly[109]. Cardiac output is estimated by multiplying heart rate by stroke volume, determined by the product of the Doppler flow velocity integral and the cross-sectional area measured at a point in the left ventricle or the aortic arch. Some investigators have obtained results with these techniques that correlate closely with thermodilution cardiac output measurements, also in pregnant patients[61,116], but others have found an unacceptable degree of random variability[56,109]. Even with refinements, the limitations inherent in estimating both blood velocity and cross-sectional area at the site of velocity measurement remain[57,158,167,240]. Doppler echocardiography has also been used as a noninvasive method to estimate mean pulmonary arterial pressure from pulsed Doppler velocities[106,114,144,186], but as yet this method has not gained wide acceptance[114]. Therefore, we consider the use of the Swan-Ganz thermodilution catheter the most appropriate method to determine central hemodynamics in obstetric patients with severe preeclampsia and other serious complications.

Chapter 3

CENTRAL HEMODYNAMIC OBSERVATIONS IN THE EARLY THIRD TRIMESTER OF UNCOMPLICATED PREGNANCY

3.1. Introduction

The development in the early seventies by Swan, Ganz and coworkers of the flow-directed, balloon-tipped and temperature-sensitive pulmonary artery catheter for bedside assessment of central venous and pulmonary intravascular pressures, and cardiac output[77,216], marks the beginning of clinical central hemodynamic monitoring, which has now become an integral part of medical and surgical intensive care. In the past decade the Swan-Ganz catheter has also been increasingly applied in the management of critically ill obstetric patients, and central hemodynamic profiles have been established of a variety of pathologic conditions in pregnancy and the early postpartum period, including cardiac disease, amniotic fluid embolism, septic shock and severe preeclampsia[15,27,32,39,82,84,91,170,176,233]. However, proper interpretation of pathophysiological central hemodynamic data is hampered by a paucity of reference values obtained in healthy women with an uncomplicated pregnancy by means of the same invasive technique. Values of central venous and pulmonary arterial pressures were determined in early cross-sectional studies in uncomplicated pregnancies using right heart catheterization[7,164], but reference values of cardiac output determined by thermodilution using the Swan-Ganz catheter are based on two reports including seven healthy parous women between 28 and 34 weeks[233], and 10 healthy nulliparous women between 36 and 38 weeks of uncomplicated pregnancy[29].

The present study was designed to assess the central hemodynamic profile and to define reference values in healthy pregnant volunteers in the early third trimester of uncomplicated pregnancy with the use of the Swan-Ganz catheter. We also studied the effects of positional changes and of food intake on cardiac output.

3.2. Subjects and methods

Selection of subjects

Twelve Caucasian parous women attending the antenatal clinic of the University Hospital Rotterdam (AZR) were recruited in the course of the second trimester of pregnancy. All were healthy, with normal weight for height; they denied a history or symptoms suggestive of cardiovascular or renal disease; they did not use drugs or tobacco; and diet was unrestricted. The women had a normal physical examination and unremarkable laboratory results. They had a singleton pregnancy with gestational age confirmed by early ultrasonography. Until the initiation of the study the course of pregnancy was uncomplicated, with maximum diastolic blood pressures of 80 mm Hg, a normally growing fetus and a normal amniotic fluid volume as assessed by repeated ultrasonography.

The purpose and design of the study were explained in detail, and all women gave their informed consent according to the requirements of the University and Hospital Ethics Committee. The volunteers were not paid for their participation in the study.

Study protocol

Between 28-30 weeks of gestational age the women were admitted to the Obstetric Intensive Care Unit at 9.00 a.m., after a light breakfast. A full physical and obstetric examination was performed, including a 12-lead electrocardiogram and a fetal cardiotocogram, with unremarkable results in all cases.

Invasive hemodynamic measurements

Each woman underwent radial and pulmonary artery catheterization, as described in Chapter 2. The pressure transducers were placed 8 cm below the level of the second intercostal space, the approximate level of the left atrium. Cardiac output was determined by thermodilution, as described in Chapter 2, in triplicate at end-expiration with an interval of approximately one minute between injections, and the arithmetic mean was taken as the final value. Maternal heart rate was derived from the electrocardiogram as the mean number of beats/min during determination of cardiac

output.

Baseline hemodynamic values were obtained after a stabilization period of 60-90 minutes, when heart rate and systemic arterial blood pressure had reached a steady state. Systemic and pulmonary intravascular pressures were determined in supine position, cardiac output was assessed in supine and left lateral position, in random order. In each woman six sets (I-VI) of measurements were performed: 60 (I) and 30 (II) minutes before lunch; 30 (III), 60 (IV), 90 (V) and 120 (VI) min. after lunch. The lunch was of standard hospital quantity and quality and contained approximately 500 kCal.

Following the last hemodynamic measurements the catheters were removed, and the women were discharged.

Data analysis

All hemodynamic variables are expressed in centimeter-gram-second (metric) units, except for pressures, which are presented in mm Hg. Resistances and central hemodynamic indexes were calculated as described in Chapter 2. Body surface area was estimated from the Dubois equation with the use of the actual height and weight of the woman. Data were evaluated with the Friedman two-way analysis of variance for repeated observations, the Wilcoxon rank-sign test, and the Spearman correlation test, as appropriate. A p-value of 0.05 (two-tailed) was taken to represent significance.

3.3. Results

Catheterizations were successful and uncomplicated in all women. After the study two women developed mild nonproteinuric pregnancy-induced hypertension, and their hemodynamic data were excluded from the analysis. In the remaining 10 women the further course of pregnancy was uncomplicated, and their clinical characteristics are summarized in Table 3.1. Nine women had uncomplicated vaginal deliveries; a cesarean section was performed in one case because of dystocia. All women were delivered of live and healthy infants with birthweights above the 10th percentile of the Dutch reference curve[107].

Table 3.1. *Clinical characteristics.*

Age (yr)	30 (24-37)
Height (cm)	167 (152-182)
Weight at measurement (kg)	73 (56-82)
Body surface area at measurement (m^2)	1.85 (1.54-2.05)
Highest diastolic blood pressure before delivery (mm Hg)	80 (75-85)
Gestational age (wk)	
at measurement	29 (28-30)
at delivery	39 (36-41)
Birthweight (g)	3300 (2270-4190)

Values are median (range).

Hemodynamic profiles before and after lunch, and combined values, of the 10 women analyzed are presented in Table 3.2. The coefficient of variation of triplicate cardiac output measurements before lunch was 6 percent, after lunch 7 percent. No differences could be demonstrated between hemodynamic values determined in supine and in left lateral position (Fig. 3.1).

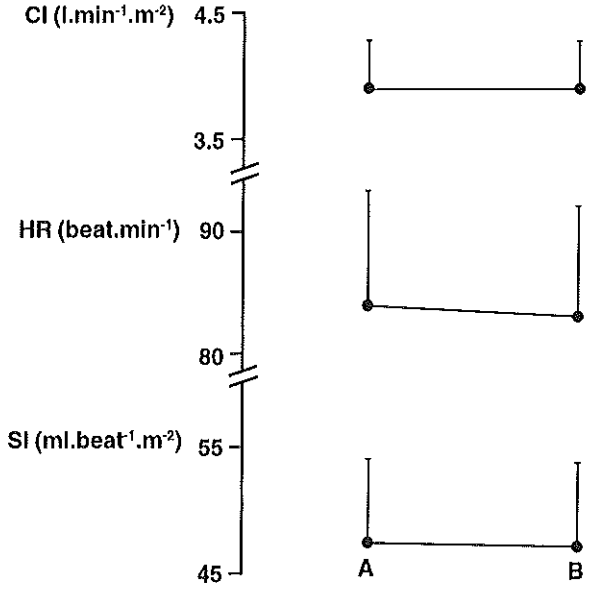


Fig. 3.1. *Mean (SD) values of cardiac index (CI), heart rate (HR) and stroke volume index (SI) obtained in supine (A) and in left lateral recumbent (B) position.*

Table 3.2. *Hemodynamic profiles before and after lunch.*

	Before lunch	p*	After lunch	All values
Systemic circulation				
Heart rate (beats.min^{-1})	78 (68-93)	< 0.05	84 (70-91)	82 (68-93)
Mean intra-arterial pressure (mm Hg)	86 (81-89)	NS	83 (81-89)	83 (81-89)
Cardiac output (l.min^{-1})	7.1 (5.9-8.1)	< 0.01	7.8 (6.1-8.8)	7.4 (5.9-8.8)
Cardiac index (l.min^{-1}.m^{-2})	3.8 (3.5-4.3)	< 0.01	4.4 (3.6-4.6)	4.2 (3.5-4.6)
Stroke volume (ml.beat^{-1})	94 (63-107)	< 0.05	96 (67-111)	96 (63-111)
Stroke volume index (ml.beat^{-1}.m^{-2})	49 (38-58)	< 0.05	52 (40-61)	51 (38-61)
Systemic vascular resistance (dyn.s.cm^{-5})	970 (826-1209)	< 0.01	841 (762-1190)	899 (762-1209)
Systemic vascular resistance index (dyn.s.cm^{-5}.m^{2})	1762(1568-2019)	< 0.01	1508(1430-1987)	1560(1430-2019)
Left ventricular stroke work index (J.beat^{-1}.m^{-2})	0.52(0.43-0.62)	NS	0.55(0.46-0.64)	0.54(0.43-0.64)
Pulmonary circulation				
Mean pulmonary arterial pressure (mm Hg)	9 (7-13)	NS	9 (7-13)	9 (7-13)
Pulmonary capillary wedge pressure (mm Hg)	4 (1-8)	NS	5 (1-8)	5 (1-8)
Right atrial pressure (mm Hg)	1 (0-2)	NS	1 (0-2)	1 (0-2)
Pulmonary vascular resistance (dyn.s.cm^{-5})	51 (34-68)	NS	62 (38-68)	57 (34-68)
Pulmonary vascular resistance index (dyn.s.cm^{-5}.m^{2})	83 (63-128)	NS	103 (71-127)	91 (63-128)
Right ventricular stroke work index (J.beat^{-1}.m^{-2})	0.06(0.04-0.07)	NS	0.05(0.04-0.08)	0.05(0.04-0.08)

Values are median (range). NS = not significant.

The supine hypotensive syndrome was not observed. No significant differences were demonstrated between the two sets of hemodynamic values (I-II) obtained before lunch, and between the four sets (III-VI) determined after lunch. Lunch did not affect systemic or pulmonary intravascular pressures. Cardiac output showed a significant rise of 14 percent caused by a significant increase in both heart rate and stroke volume. These changes were sustained during the two hours of follow-up (Fig. 3.2).

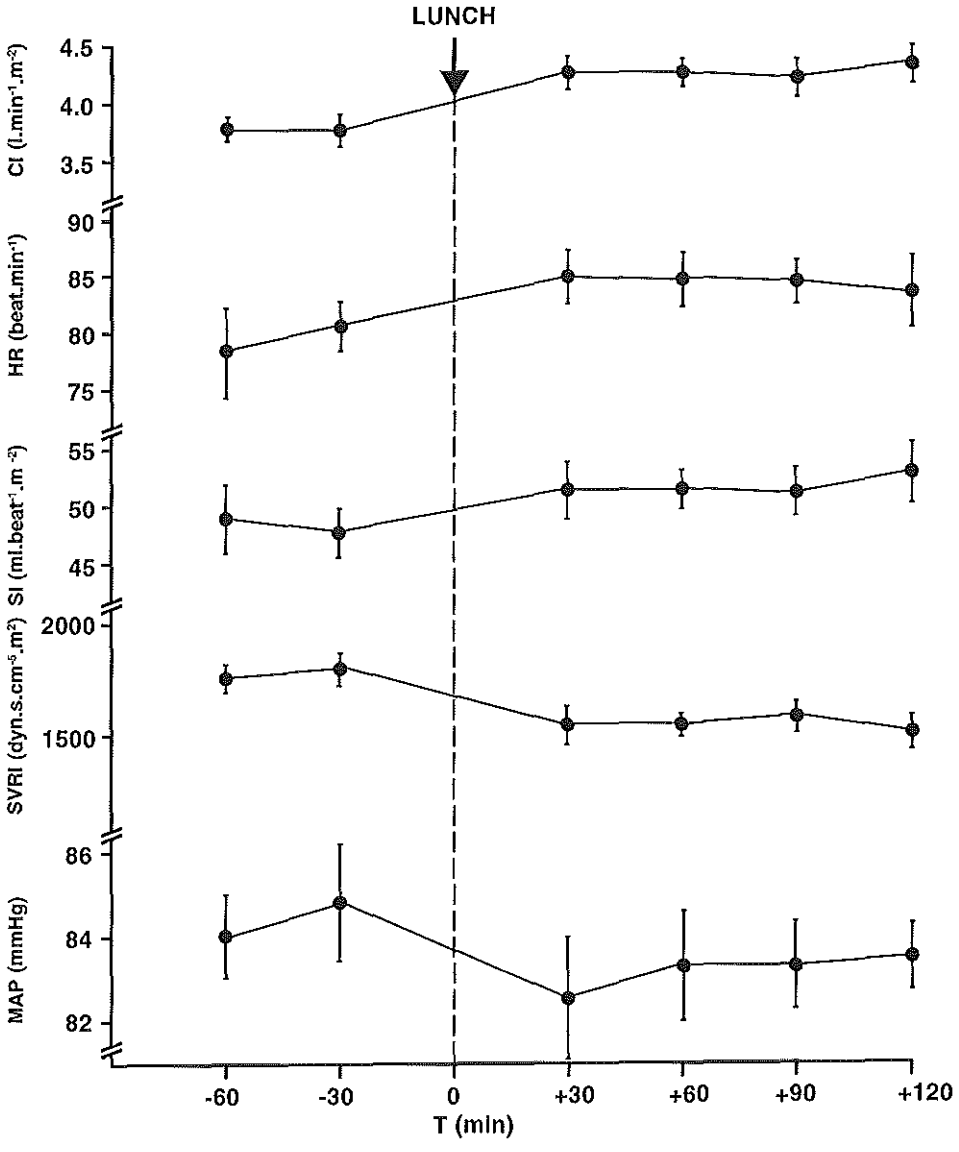


Fig. 3.2. *Mean (SD) hemodynamic values obtained before (-60, -30 min) and after (+30 - +120 min) a standard 500 kCal lunch.*

A plot of left ventricular stroke work index and pulmonary capillary wedge pressure shows that mean values of seven of the 10 women fall to the left of the physiological left ventricular function curve based on data obtained in nonpregnant individuals[188] (Fig. 3.3.).

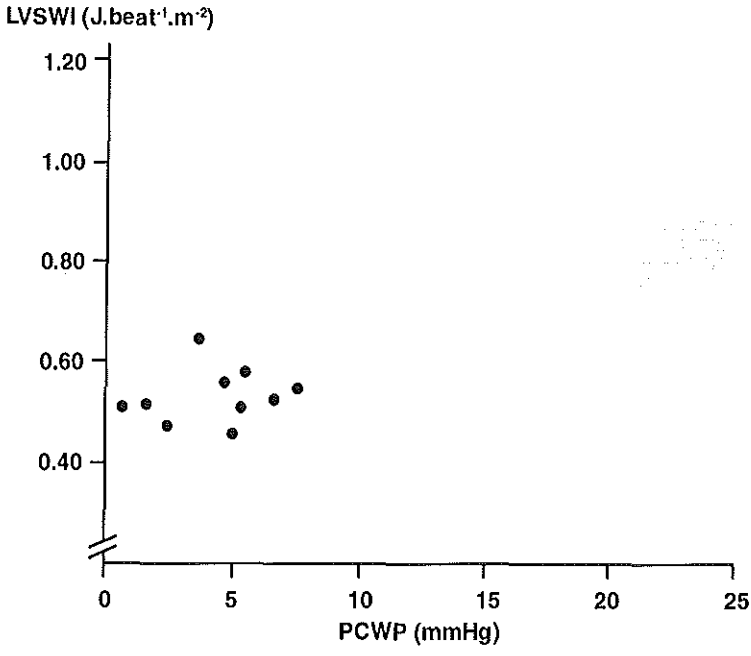


Fig. 3.3. *Scatterplot of left ventricular stroke work index (LVSWI) against pulmonary capillary wedge pressure (PCWP). Each dot represents the mean value of 6 sets of measurements in each woman. The boundaries of physiological nonpregnant left ventricular function as indicated by the shaded area, are modified from Ross and Braunwald[188].*

A plot of individual mean cardiac output values against estimated body surface areas shows a significant positive linear correlation (Fig. 3.4).

3.4. Discussion

There is general agreement that uncomplicated pregnancy is associated with minor changes in systemic and pulmonary intravascular pressures, whereas cardiac output shows an increase of 1.5-2 $l.min^{-1}$ that is accomodated by a marked fall in vascular resistance[230]. For that reason, central hemodynamic assessment in obstetric

patients cannot be based on hemodynamic data derived from nonpregnant subjects, but requires reference values obtained in a carefully selected pregnant population. Central hemodynamic monitoring using the Swan-Ganz catheter has become the method that is generally used in an intensive care setting, also for critically ill obstetric patients[4,127,232].

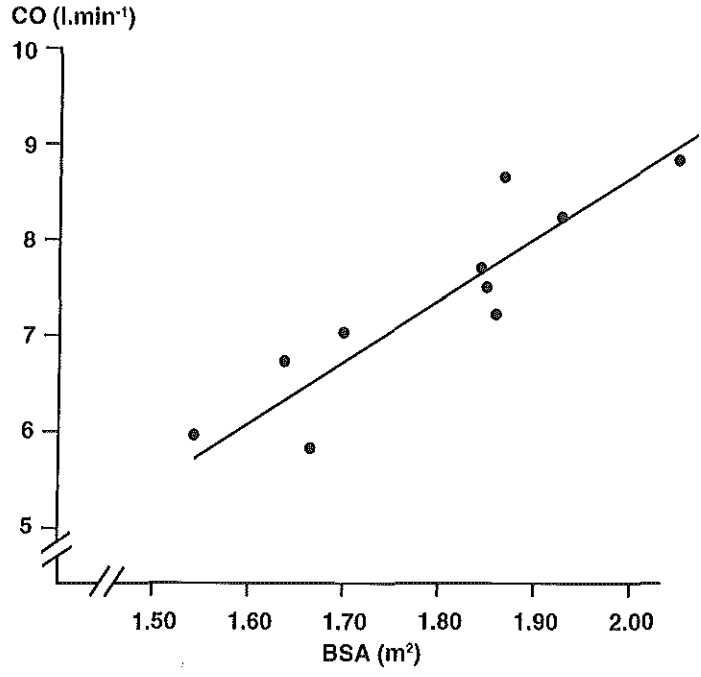


Fig. 3.4. *Correlation between cardiac output (CO) and estimated body surface area (BSA). Each dot represents the mean value of 6 sets of determinations of cardiac output in each woman. Correlation coefficient r=0.89 ($p < 0.001$).*

The Swan-Ganz technique allows the clinician serial measurements of pulmonary intravascular pressures and cardiac output easily, quickly, and reliably[35,67,153]. Although two noninvasive techniques, transthoracic impedance and combined Doppler-ultrasound, allow cardiac output to be determined noninvasively, these methods lack the ability of simultaneous measurement of intravascular pressures, which is indispensable in the

assessment of overall patient hemodynamic status, and their reliability is questionable[113,114]. Because of the paucity of central hemodynamic reference values for the physiological pregnant state obtained by means of the Swan-Ganz technique, we felt that there was an urgent need for the invasive study in healthy pregnant volunteers reported in this chapter.

The hemodynamic data obtained in our study are slightly different from those reported in the two earlier studies in which the Swan-Ganz catheter was used (Table 3.3).

Table 3.3. *Comparison between reference values of central hemodynamics assessed by means of invasive hemodynamic monitoring in healthy normotensive pregnant women in the present study and in two earlier reports.*

	Wallenburg 1988[233]	This thesis		Clark et al. 1989[29]
	Median (range)	Median (range)	Mean (S.D)	Mean (S.D)
Number of women (n)	7	10		10
Age (yr)	25 (22-38)	30 (24-37)		< 26
Parity	Parous	Parous		Nulliparous
Gestational age (wks)	28 (28-34)	29 (28-30)		36-38
Systemic circulation				
Heart rate ($beat.min^{-1}$)	80 (67-93)	82 (68-93)	82 (8.6)	83 (10)
Mean intra-arterial pressure (mm Hg)	83 (70-100)	83 (81-89)	84 (2.3)	90.3 (5.8)
Cardiac output ($l.min^{-1}$)	?	7.4 (5.9-8.8)	7.4 (1.0)	6.2 (1.0)
Cardiac index ($l.min^{-1}.m^{-2}$)	4.0 (3.9-5.0)	4.2 (3.5-4.6)	4.1 (0.3)	?
Systemic vascular resistance ($dyn.s.cm^{-5}$)	?	899 (762-1209)	907 (143)	1210 (266)
Systemic vascular resistance index ($dyn.s.cm^{-5}.m^{2}$)	1629(1197-1838)	1560(1430-2019)	1612 (168)	?
Left ventricular stroke work index ($J.beat^{-1}.m^{-2}$)	?	0.54(0.43-0.64)	0.54 (0.06)	0.48 (0.06)
Pulmonary circulation				
Pulmonary capillary wedge pressure (mm Hg)	6 (3-12)	5 (1-8)	4.3 (2.2)	7.5 (1.8)
Right atrial pressure (mm Hg)	4 (1-9)	1 (0-2)	1 (0.9)	3.6 (2.5)

? = not reported

The small differences in systemic and pulmonary intravascular pressures may be explained by interindividual variability, but also by differences in transducer position. Whereas we always placed the pressure transducers 8 cm below the level of the second intercostal space, Clark et al.[29] positioned the transducers at the level of the left atrium as determined by realtime echocardiography. Because the pulmonary capillary wedge pressures observed in our study are lower and values of LVSWI are slightly higher than those reported in the earlier studies (Table 3.3.), the plot of the left ventricular function curve tends to fall to the left of the physiological Frank Starling curve based on measurements in healthy nonpregnant individuals. This hyperdynamic myocardial state indicates that the left ventricle in normotensive pregnancy functions effectively at relatively low filling pressures.

The sum of biologic and methodologic variance of 6-7 percent for the measurements of cardiac output in triplicate attained in our study is in agreement with reports in the literature[35,153]. Cardiac output values in our study are similar to those reported by Wallenburg[233], but approximately 20 percent higher than determined by Clark et al.[29], with a similar heart rate. The difference may be related to the fact that gestational age in the 10 women studied by Clark et al.[29] was about eight weeks longer than that in our group of pregnant volunteers. Results of longitudinal studies using Doppler echocardiography indicate that cardiac output decreases after approximately 35 weeks' gestation due to a fall in stroke volume, whereas heart rate remains constant[64,146].

It is generally accepted that the physiological increase in circulating volume and cardiac output in pregnancy is independent of prepregnancy values[96,230]. Indexing by body surface area based on the Dubois equation using height and body weight may eliminate the factor of variation in prepregnancy cardiac output related to body mass and may thus allow a more realistic comparison between individuals. Unfortunately, a reliable estimate of prepregnancy weight was not available in most cases and for that reason we used the actual weight at the time of measurement for the estimation of body surface area. Nevertheless, we found an excellent correlation between body surface area and cardiac output, suggesting similar weight gain in all women. Care should be taken to index hemodynamic values by body surface area based on actual bodyweight in pregnant women with abnormal weight gain, e.g. because of edema, as may be

expected in patients with a pregnancy-induced hypertensive disorder.

When a pregnant woman lies flat on her back, the heavy gravid uterus in the second half of pregnancy may compress the aorta and vena cava, with a consequent fall in cardiac output[104,147,230]. The degree of aortocaval compression depends on a variety of factors[147]. The actual effect of recumbent postural change on cardiac output is determined by the balance of the degree of vascular compression and of circulatory adjustments such as the paravertebral collateral venous return to the heart, and appears to be variable and relatively small[63,117,157,223]. In their recent study in 10 healthy primiparous women with normotensive term pregnancy Clark et al.[30], using the direct Fick technique, found a 9 percent higher cardiac output in left lateral compared with supine position, a difference within the precision of 5-10 percent achieved in most clinical conditions with the method used[220]. We found no consistent differences between cardiac outputs in left lateral and supine position in any of the six sets of measurement, which supports the concept that positional aortocaval compression is balanced by hemodynamic adjustments in the majority of pregnant women.

Eating is a less well recognized cause of variability of cardiac output[40,244]. The increase in gut blood flow after a meal will be met by an increase in cardiac output and redistribution of organ flows, which may explain the clinical observation that some cardiovascular diseases are aggravated by eating[244]. The present study provides the first data on the effect of a light hospital lunch on cardiac output in healthy pregnant women. We observed a 14 percent increase in cardiac output after lunch, due to a combined rise in heart rate and stroke volume. The increase in cardiac output observed in our study was less pronounced than that of 30 percent in a study in nonpregnant subjects[40], but that effect was obtained after a festive Christmas lunch of 1400 kCal. Also in pregnant women a heavier meal than that used in our study may have a more marked impact on cardiac output. The results of our study indicate a need for further assessment of the effects of eating on maternal hemodynamics in uncomplicated gestation as well as in pregnancies complicated by a hemodynamic disorder such as preeclampsia.

Chapter 4

CENTRAL HEMODYNAMIC OBSERVATIONS IN UNTREATED PREECLAMPTIC PATIENTS*

4.1. Introduction

Over the past 10 years, at least eight reports have been published in the English literature on the results of central hemodynamic measurements obtained in preeclamptic patients with the flow-directed, thermistor-tipped Swan-Ganz pulmonary artery catheter[15,33,39,82,126,170,176,215]. The reports show marked disparity with regard to cardiac output, peripheral vascular resistance, and left ventricular filling pressures, with values covering a wide spectrum between the extremes of a high-output, low-resistance and a low-output, high-resistance hemodynamic state. The observed hemodynamic variability usually is attributed to a variable pathophysiological expression of the pregnancy-induced hypertensive disorder[15,33,39,170].

Close examination reveals that, with a single exception[82], all studies were carried out during or after pharmacologic treatment consisting of magnesium sulfate, antihypertensive medication, and intravenous fluids. In addition, variables which may modulate the hemodynamic state - such as parity, labor, underlying cardiac, renal or hypertensive disease, and the severity of the hypertensive disorder - were not taken into account in the majority of published studies.

The present study was done to test the hypothesis that the reported hemodynamic variability in preeclampsia is mainly secondary to treatment rather than reflecting a variable pathophysiological state. We compared the results of central hemodynamic measurements in patients with untreated severe antepartum preeclampsia in the second or early third trimester of pregnancy with those obtained in patients with preeclampsia of similar severity in the same gestational period who already had received pharmacologic treatment.

* *The main substance of this chapter was published in: Visser W, Wallenburg HCS. Central hemodynamic observations in untreated preeclamptic patients. Hypertension 1991; 17:1072-1077.*

4.2. Subjects and methods

Selection of patients

A group of 134 consecutive pregnant patients with severe preeclampsia was studied. All patients were managed between 1985 and 1990 in the Department of Obstetrics of the University Hospital Rotterdam (AZR) and all met the following inclusion criteria: 1) gestational age less than 34 weeks; 2) singleton pregnancy with a live fetus; 3) no maternal or fetal indication for immediate delivery as judged by the attending obstetrician; 4) unrestricted diet; 5) not in labor; 6) no signs of pulmonary edema, and 7) no known preexisting hypertensive, cardiac, or renal disease. Severe pre-eclampsia was defined as the occurrence of a diastolic blood pressure of 100 mm Hg or more on two occasions at least 4 hours apart and proteinuria of 0.5 g/L or more in a 24 hour urine collection. All patients had developed preeclampsia after the 20th week of gestation and became normotensive and nonproteinuric after delivery.

Before the start of hemodynamic investigations patients who had not received any kind of pharmacologic treatment, including parenteral administration of fluids, were labeled untreated. Patients who already had received intravenous fluids or any kind of antihypertensive or anticonvulsive treatment were labeled treated. The study protocol as approved by the University and Hospital Ethics Committee was explained in detail, and informed consent was obtained in all cases.

Invasive hemodynamic measurements

A normal baseline electrocardiogram was obtained from all patients. A radial artery was cannulated for intra-arterial blood pressure measurement and a Swan-Ganz pulmonary artery catheter was inserted as described in detail in Chapter 2. The catheterizations were performed without the use of analgesics or sedatives. Measurements, as described in detail in Chapter 2, were begun at least one hour, usually longer, after catheterization, when heart rate and systemic arterial blood pressure had reached a steady state. Maternal heart rate was determined from the continuously recorded electrocardiogram. Right atrial and pulmonary pressures were determined with the patient in supine position; cardiac output was determined in triplicate at end-expiration, with the patient in supine and in left lateral position.

Study protocol

At least four measurements of cardiac output and pulmonary capillary wedge pressure were performed in each patient, and the arithmetic mean was taken as the representative value of each hemodynamic variable. Patients were pharmacologically treated or delivered following the hemodynamic measurements. The Swan-Ganz catheter was removed within 72 hrs of insertion in all cases.

Data analysis

All hemodynamic variables are expressed in centimeter-gram-second (metric) units, except for blood pressures which are presented in millimeters of mercury. Resistances and indexes of left ventricular stroke work were calculated as described in Chapter 2. Data are presented as median and range, unless stated otherwise. Differences were statistically analyzed with the Wilcoxon test, and the significance of correlations was tested with the Spearman test. Because of multiple comparisons a p-value of less than 0.01 (two-tailed) was taken as the level of significance.

4.3. Results

Insertion and maintenance of the radial artery and Swan-Ganz catheters were successful and uncomplicated in all patients.

Clinical characteristics

Clinical characteristics of the 134 preeclamptic patients included in the study are summarized in Table 4.1. The majority of the 47 treated patients were maternal transfers from other hospitals, who had received dihydralazine, magnesium sulfate, diazepam or a variety of other drugs and intravenous fluids. There were no significant differences between groups with regard to any of the maternal characteristics, gestational age or severity of the hypertensive disorder. Also presented in Table 4.1. are the clinical characteristics of the 10 normotensive parous women with uncomplicated pregnancies reported in Chapter 3, from whom reference values for central hemodynamic variables were obtained. Maternal variables, with the exception of those related to preeclampsia, in the normotensive pregnant women, were comparable with those in the preeclamptic patients.

Table 4.1. *Clinical characteristics of 134 preeclamptic patients.*

	Preeclamptic untreated		Preeclamptic treated		Normotensive
	nulliparous (n=74)	parous (n=13)	nulliparous (n=32)	parous (n=15)	parous (n=10)
Age (yr)	26 (18-42)	27 (21-37)	26 (19-41)	28 (19-44)	30 (24-37)
Gestational age (wk)	30.4(25.3-33.6)	31.3(25.1-33.9)	29.1(26.1-33.9)	29.0(24.9-33.6)	28.9(28.0-30.4)
Body surface area (m^2)	1.79(1.37-2.16)	1.73(1.55-2.20)	1.86(1.57-2.03)	1.77(1.43-1.98)	1.85(1.54-2.05)
Diastolic blood pressure (mm Hg)	110 (100-140)	115 (100-130)	110 (100-140)	115 (100-150)	75 (70-80)*
Proteinuria ($g.l^{-1}$)	3.0 (0.5-25.3)	1.9 (0.5-14.2)	3.0 (0.5-39.3)	3.8 (0.5-23.1)	-

Values are median (range).

* $p < 0.01$ compared with preeclamptic patients.

Hemodynamic measurements

The hemodynamic findings in untreated and treated nulliparous and parous preeclamptic patients are shown in Table 4.2. There were no differences between cardiac output values measured with patients in supine and in left lateral position. There was a significant ($p < 0.0001$) positive correlation between cardiac output and body surface area in all groups. We found no significant differences in hemodynamic variables within groups between nulliparous and parous patients. We found no significant correlations between arterial pressures and cardiac index. Comparison between all treated and untreated preeclamptic women showed a significantly lower cardiac index and stroke volume index, and a higher systemic vascular resistance index in untreated patients. Statistical testing of differences in indexed stroke volume and systemic vascular resistance between treated and untreated parous patients gave a p-value of 0.01, not statistically significant according to the definition. Also, pulmonary vascular resistance was higher in untreated than in treated patients, although the difference between parous patients did not reach significance. Left ventricular filling pressures were not different between groups.

Table 4.2. *Hemodynamic profiles in untreated and treated patients with severe preeclampsia.*

	Untreated			Treated		
	nulliparous (n=74)	p	parous (n=13)	nulliparous (n=32)	p	parous (n=15)
Systemic circulation						
Heart rate ($beats.min^{-1}$)	74 (57-110)	NS	78 (51-95)	84 (64-131)*	NS	87 (62-135)
Mean intra-arterial pressure (mm Hg)	125 (92-156)	NS	123 (96-143)	120 (80-138)	NS	120 (105-154)
Cardiac index ($l.min^{-1}.m^{-2}$)	3.4 (2.1-5.3)	NS	3.1 (2.0-4.2)	4.3 (3.0-7.6)*	NS	3.8 (2.4-7.0)**
Stroke volume index ($ml.beat^{-1}.m^{-2}$)	48 (25-75)	NS	35 (29-56)	52 (32-82)*	NS	52 (33-65)***
Systemic vascular resistance index ($dyn.s.cm^{-5}.m^2$)	2951 (1771-5225)	NS	3331 (1827-4753)	2162 (1057-3325)*	NS	2581*** (1177-3688)
Left ventricular stroke work index ($J.beat^{-1}.m^{-2}$)	0.71(0.40-1.16)	NS	0.63(0.45-0.85)	0.81(0.48-1.27)	NS	0.72(0.52-1.06)
Pulmonary circulation						
Mean pulmonary arterial pressure (mm Hg)	12 (3-26)	NS	12 (3-18)	13 (5-29)	NS	12 (1-30)
Pulmonary capillary wedge pressure (mm Hg)	7 (-1-20)	NS	5 (0-13)	7 (1-20)	NS	6 (0-25)
Right atrial pressure (mm Hg)	2 (-4-10)	NS	1 (-3-6)	1 (-3-12)	NS	2 (-3-12)
Pulmonary vascular resistance index ($dyn.s.cm^{-5}.m^2$)	130 (47-278)	NS	153 (48-379)	99 (29-181)*	NS	114 (8-317)
Right ventricular stroke work index ($J.beat^{-1}.m^{-2}$)	0.06(0.01-0.20)	NS	0.05(0.01-0.10)	0.08(0.03-0.22)±	NS	0.07(0.08-0.15)

Values are median (range). NS = not significant.

* $p < 0.01$ versus untreated nulliparous patients. ± $p = 0.01$ versus untreated nulliparous patients.
** $p < 0.01$ versus untreated parous patients. *** $p = 0.01$ versus untreated parous patients.

Hemodynamic reference values obtained in 10 normotensive parous women with an uncomplicated pregnancy between 28 and 31 weeks' duration (Chapter 3) are shown in Table 4.3. in comparison with the hemodynamic variables observed in untreated and treated preeclamptic patients. In untreated preeclamptic patients cardiac indexes are significantly lower, and systemic and pulmonary vascular resistances are significantly

Table 4.3. *Hemodynamic profiles in untreated and treated preeclamptic patients, and in normotensive pregnant women.*

	Preeclamptics untreated (n=87)	p*	Normotensive controls (n=10)	p**	Preeclamptics treated (n=47)
Systemic circulation					
Heart rate ($beats.min^{-1}$)	74 (51-110)	NS	82 (68-93)	NS	85 (62-135)±
Mean intra-arterial pressure (mm Hg)	125 (92-156)	< 0.001	83 (81-89)	< 0.001	120 (80-154)
Cardiac index ($l.min^{-1}.m^{-2}$)	3.3 (2.0-5.3)	< 0.001	4.2 (3.5-4.6)	NS	4.3 (2.4-7.6)±
Stroke volume index ($ml.beat^{-1}.m^{-2}$)	46 (25-75)	NS	51 (38-61)	NS	52 (32-82)±
Systemic vascular resistance index ($dyn.s.cm^{-5}.m^{2}$)	3003(1771-5225)	< 0.001	1560(1430-2019)	< 0.005	2212(1057-3688)±
Left ventricular stroke work index ($J.beat^{-1}.m^{-2}$)	0.70(0.40-1.16)	< 0.005	0.54(0.43-0.64)	< 0.001	0.79(0.48-1.27)
Pulmonary circulation					
Mean pulmonary arterial pressure (mm Hg)	12 (3-26)	NS	9 (7-13)	< 0.01	13 (0.5-30)
Pulmonary capillary wedge pressure (mm Hg)	7 (-1-20)	NS	5 (1-8)	NS	7 (0-25)
Right atrial pressure (mm Hg)	2 (-4-10)	NS	1 (0-2)	NS	1 (-3-12)
Pulmonary vascular resistance index ($dyn.s.cm^{-5}.m^{2}$)	131 (47-379)	< 0.005	91 (63-128)	NS	101 (8-317)±
Right ventricular stroke work index ($J.beat^{-1}.m^{-2}$)	0.06(0.01-0.20)	NS	0.05(0.04-0.08)	NS	0.08(0.01-0.22)±

Values are median (range).
* p-value refers to differences between untreated preeclamptic patients and normotensive controls.
** p-value refers to differences between pharmacologically treated preeclamptic patients and normotensive controls.
± $p < 0.01$ compared with untreated preeclamptic patients.
NS = not significant.

higher than in normotensive pregnant women. In contrast, the median cardiac index in treated preeclamptic patients is similar to that determined in normotensive controls. The hemodynamic differences between treated and untreated preeclamptic patients, and normotensive pregnant controls are also apparent in Figures 4.1 and 4.2, A and B, in which the cardiac indexes are plotted against systemic and pulmonary perfusion pressures. In Fig. 4.3A, mean values of pulmonary capillary wedge pressure and left ventricular stroke work index (LVSWI) in untreated preeclamptic women are plotted in a physiological left ventricular function curve (Starling plot) based on measurements in healthy nonpregnant individuals[188]. Values are shifted upward and to the left, indicating hyperdynamic function of the left ventricle in the majority of patients. Fig. 4.3B shows left ventricular function in treated preeclamptic women. In comparison with the untreated group, left ventricular function appears to be more variable; three patients have LVSWI values to the right of the curve, indicating impending left ventricular failure.

4.4. Discussion

To the best of our knowledge this is the first study, after preliminary data published by our group[82,233], of central hemodynamics measured with a Swan-Ganz catheter in completely untreated nulliparous and parous preeclamptic patients who developed what may be most likely defined as "pure preeclampsia". Chronic hypertension may have a marked influence on central hemodynamics[124], but we excluded such women in the selection of our patient population. Because it has been shown, particularly in parous women with preeclampsia, that there is often an unsuspected underlying hypertensive or renal disease[120], only patients who became normotensive and nonproteinuric after delivery were included in our study.

The absence of labor is a prerequisite for the assessment of the true pathophysiological hemodynamic state in preeclamptic patients. Uterine contractions are known to cause marked hemodynamic changes, most likely because of the autotransfusion effect of blood squeezed out of the contracting uterus[222]. Indeed, hemodynamic studies in preeclamptic patients have shown a dramatic rise in cardiac output, and in systemic and pulmonary blood pressures during labor and delivery[170,176]. Therefore, patients who were in labor also were excluded.

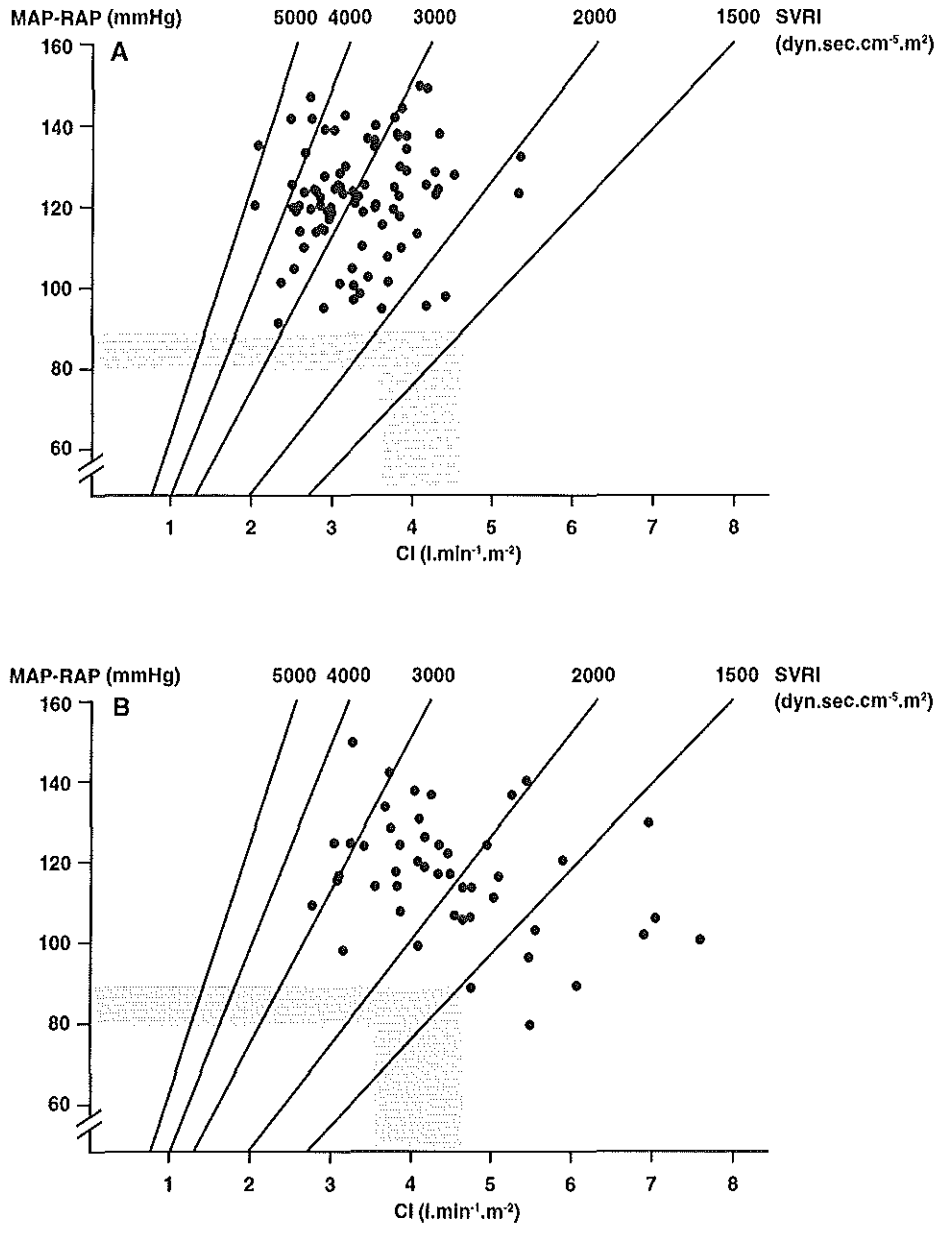
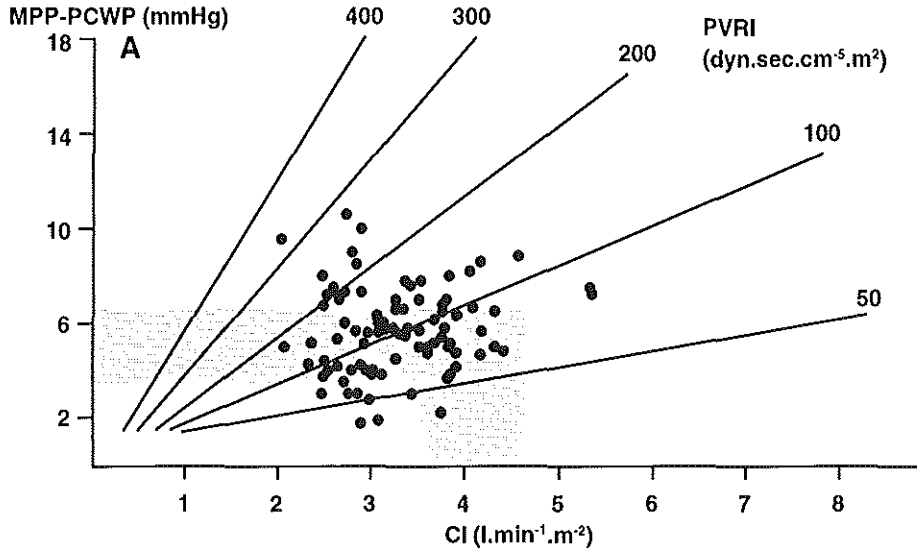


Fig. 4.1. *Relationship between systemic perfusion pressure (MAP-RAP), cardiac index (CI), and systemic vascular resistance index (SVRI) in 87 untreated (panel A) and 47 treated (panel B) preeclamptic patients. Values for normotensive pregnant women fall within the shaded area.*



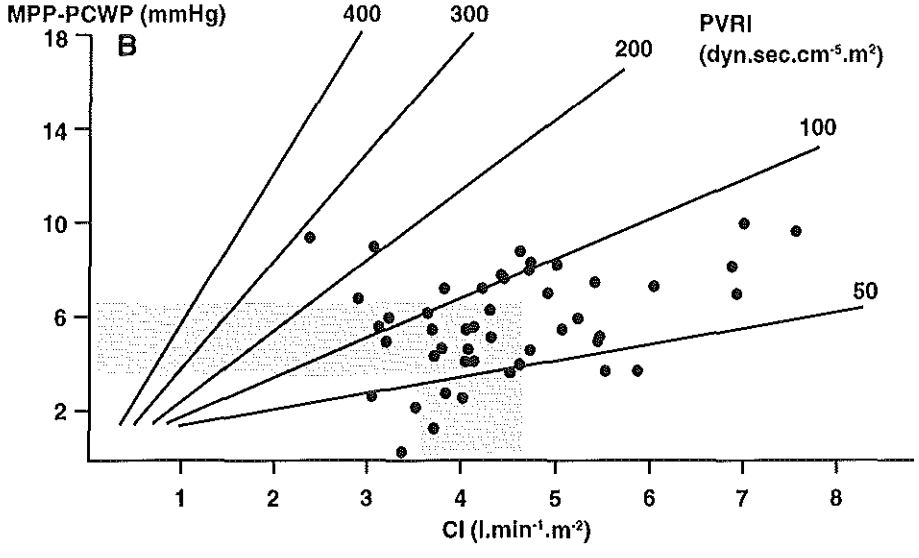


Fig. 4.2. *Relationship between pulmonary perfusion pressure (MPP-PCWP), cardiac index (CI), and pulmonary vascular resistance index (PVRI) in 87 untreated (panel A) and 47 treated (panel B) preeclamptic patients. Values for normotensive pregnant women fall within the shaded area.*

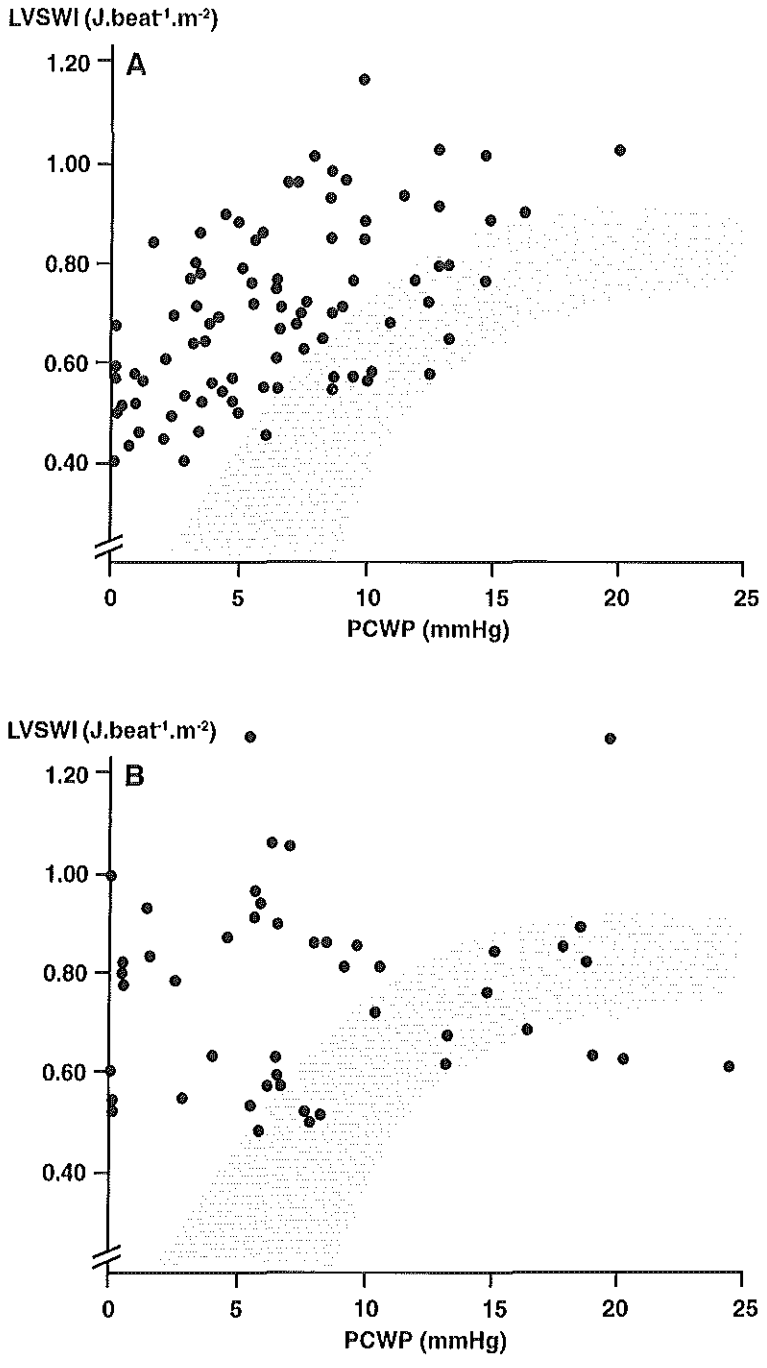


Fig. 4.3. *Scatterplots showing left ventricular stroke work index (LVSWI) in 87 untreated (panel A) and 47 treated (panel B) preeclamptic patients plotted against pulmonary capillary wedge pressure (PCWP). The boundaries of normal nonpregnant left ventricular function, as indicated by the shaded area, are modified from Ross and Braunwald[188].*

Because the technique used for measuring central hemodynamics also could be an important variable, we will compare our results only with those obtained in other studies that used a Swan-Ganz catheter. Our results show that parity has no demonstrable effect on hemodynamic findings. It therefore is unlikely that heterogeneity with regard to parity is an important factor underlying the reported hemodynamic disparity in preeclampsia.

We found no significant differences between cardiac output measured with patients in supine or in left lateral position. This is in agreement with our observations in normotensive women in the early third trimester of pregnancy reported in Chapter 3, and with data from other studies in which the impediment of venous return through the vena cava caused by the gravid uterus appeared to be minimal[63,117,157,223].

In contrast to the rather uniform pattern of a low cardiac index, and a high systemic vascular resistance in untreated preeclamptic patients, we found a wide range of hemodynamic values in treated preeclamptic women, with even extremely high cardiac indexes and low systemic resistances in these patients. The different hemodynamic profile in treated and untreated patients is also clearly demonstrated in the left ventricular Starling plot. Since patients in both groups were similar with regard to clinical characteristics and severity of the preeclamptic state, the differences in hemodynamic profile could most likely be attributed to the administration of drugs and intravenous fluids in the treated group, whereas the untreated patients received no more than 20-30 ml of saline for insertion and flushing of the catheters. All preeclamptic women reported in previous hemodynamic studies, except one[82], had received and were receiving intravenous magnesium sulfate, a drug known to increase cardiac output to a marked but variable extent[37,151]. In addition to the use of antihypertensive drugs, this may explain a large part of the reported hemodynamic variability and tendency to a high cardiac output in preeclamptic patients.

Some authors[62,126] suggest that cardiac output may increase in the beginning of the development of preeclampsia and could fall with increasing severity of the disease. Our findings do not support that hypothesis. First, we found no correlation between the height of the diastolic blood pressure and the cardiac output. Second, diastolic blood pressures and the amount of proteinuria in our patients are similar to those reported in the literature in preeclamptic patients with high cardiac outputs[39,126].

From our hemodynamic observations in untreated patients, we conclude that severe preeclampsia is hemodynamically characterized by a low cardiac output in the presence of an increased left ventricular afterload. Although untreated preeclamptic patients also show some variability in the hemodynamic expression of the disease, the reported extremes of the hemodynamic profile appear to reflect clinical management rather than the pathophysiological state.

There is general agreement that plasma volume is reduced in these patients[88], but we found no evidence of a significant reduction in cardiac preload. This may be explained in part by the relative insensitivity of our hemodynamic measurements. On the other hand, a reduced vascular capacitance due to venoconstriction[124] with redistribution of intravascular volume from the splanchnic to the peripheral vascular bed cannot be excluded.

CHAPTER 5

HEMODYNAMIC EFFECTS OF PLASMA EXPANSION AND VASODILATATION IN PREECLAMPTIC PATIENTS

5.1. Introduction

The vasodilators hydralazine and dihydralazine are the most frequently used agents to treat hypertension in pregnant patients with severe preeclampsia[43,54,111]. However, the pronounced arteriolar dilatation which, together with some dilatation of the venous vascular system, is responsible for the reduction in arterial blood pressure, may also cause a marked decrease in the degree of filling of the circulatory system and hence in the venous return to the heart, which cannot always be compensated for by circulatory reflexes and may lead to shock-like hemodynamic decompensation[111,233]. Preeclamptic women often have a contracted plasma volume[23,74,88] and appear to be especially sensitive to the vasodilator effects of (di)hydralazine[23,55]. In a preliminary study in a small group of preeclamptic patients Wallenburg[233], using central hemodynamic monitoring by means of a Swan-Ganz catheter, showed that these adverse effects of dihydralazine may be avoided by combining the administration of dihydralazine with plasma volume expansion. The present study is a continuation of that investigation designed to further assess the systemic and pulmonary hemodynamic effects of dihydralazine infusion in preeclamptic patients with and without plasma volume expansion.

5.2 Subjects and Methods

Selection of patients

Thirty-eight patients with preeclampsia admitted to the antenatal wards of the University Hospital Rotterdam (AZR) in the third trimester of pregnancy were studied. All patients met the following criteria: 1) gestational age less than 34 weeks; 2)

singleton pregnancy with a live fetus; 3) no maternal or fetal indication for immediate delivery as judged by the attending obstetrician; 4) unrestricted diet; 5) no antihypertensive or anticonvulsant therapy; 6) not in labor; 7) no known preexisting hypertensive, cardiac, or renal disease. Preeclampsia was defined as the occurrence after 20 weeks' gestation of a diastolic blood pressure of 100 mm Hg (Korotkoff 4) or more on two occasions at least 4 hours apart and proteinuria of 0.3 g/l or more in a 24 hour urine collection. Gestational age was based on the last menstrual period and confirmed by early ultrasound in all cases.

The study protocol as approved by the University and Hospital Ethics Committee was explained in detail and we obtained informed consent from each patient.

Maternal and fetal monitoring

The studies were performed in the Obstetric Intensive Care Unit. A normal baseline electrocardiogram was obtained from all patients. Systemic arterial pressures were measured by means of a radial artery catheter and a pulmonary artery (Swan-Ganz) catheter was inserted in all patients for measurement of pulmonary pressures and determination of cardiac output by thermodilution (Chapter 2). Maternal heart rate was determined from the continuously recorded electrocardiogram. All patients received a bladder catheter to determine hourly urine output. Fetal size and growth were assessed by ultrasound and fetal condition during the study was monitored continuously by Doppler ultrasound cardiotocography.

Study Protocol

Baseline hemodynamic measurements

Baseline hemodynamic values determined before the experiments included systemic and pulmonary arterial pressures, right atrial (RAP) and pulmonary capillary wedge (PCWP) pressures, heart rate (HR), cardiac output (CO) and calculated systemic and pulmonary vascular resistances. All measurements were carried out with the patients in supine position. Values used for analysis were obtained after a stabilization period of at least one hour after catheterization, when heart rate and systemic arterial blood pressure had reached a steady state.

Vasodilatation followed by volume expansion (group I)

In order to assess the hemodynamic effects of pharmacologic vasodilatation we selected 19 preeclamptic patients (group I) with a urine output of at least 30 ml/hr. After baseline hemodynamic values were obtained, the patients received an intravenous infusion of dihydralazine with a starting dose of 1 mg/hr, followed by half-hourly increments of 0.5 mg, until a diastolic intra-arterial blood pressure of approximately 90 mm Hg was reached, or urine production decreased to less than 30 ml/hr, or fetal distress occurred. Thereafter, dihydralazine infusion was continued at the same rate and the patients were volume expanded with pasteurized plasma at a rate of approximately 250 ml/hr until a PCWP of 10 mm Hg was obtained. In patients in whom fetal distress occurred infusion of dihydralazine was reduced or temporarily stopped.

Volume expansion followed by vasodilatation (group II)

In 19 preeclamptic patients (group II), circulating volume was expanded with pasteurized plasma at a rate of approximately 250 ml/hr to reach and maintain PCWP values of 10 mm Hg. Thereafter, dihydralazine was infused at a rate of 1 mg/hr, followed by half-hourly increments of 0.5 mg, until the intra-arterial diastolic blood pressure was approximately 90 mm Hg. In contrast to the protocol applied in group I, oliguric patients with a urine production below 30 ml/hr were not excluded from group II.

Hemodynamic measurements during treatment.

In both groups we determined systemic and pulmonary pressures, and heart rate continuously during the study, and measured PCWP and CO before the start of plasma or dihydralazine infusion and every 30 minutes thereafter. PCWP and CO were also determined before every increment or decrease in the dose of dihydralazine and after a diastolic blood pressure of 90 mm Hg was reached. All measurements were done with the patient in supine position. Apart from dihydralazine or pasteurized plasma no drugs, including magnesium sulfate or diazepam, were administered during the study. When in the second part of the protocol a PCWP of 10 mm Hg (group I) or an intra-arterial diastolic blood pressure of 90 mm Hg (group II) was obtained, the experiments were terminated. The Swan-Ganz catheter was removed within 72 hrs of insertion in all cases

and patients were managed conservatively as reported in Chapter 6.

Data analysis

All hemodynamic variables are expressed in centimeter-gram-second (metric) units, except for blood pressures, which are presented in millimeters of mercury. Resistances and indexes of ventricular stroke work were calculated as described in Chapter 2. Hemodynamic values after treatment are the maximum effects observed. Data are presented as mean and standard deviation, unless stated otherwise.

We used Student's t-test for independent samples for comparison of continuous variables between groups, and the t-test for paired samples for comparison within groups. Categorical variables were assessed with the χ^2-test or Fisher's exact test. Because of multiple comparisons a p-value of less than 0.01 (two-tailed) was taken to represent statistical significance.

5.3. Results

Clinical characteristics

As shown in Table 5.1. there were no differences between the clinical characteristics of the two groups.

Table 5.1. *Clinical characteristics of preeclamptic patients in both groups.*

	Group I (n=19)	Group II (n=19)
Age (yrs)	27±5.5	27±4.2
Nulliparous	16	17
Gestational age (wks)	30.7±3.04	30.5±3.01
Body surface area (m^2)	1.81±0.12	1.76±0.18
Systolic blood pressure (mm Hg)	175±16.8	168±12.2
Diastolic blood pressure (mm Hg)	118±10.4	117±8.9
Proteinuria		
0.3-5 g/l	13	13
≥ 5 g/l	6	6
Urine production (ml/hr)	95±61.5	61±33.6
Urine production < 30 (ml/hr)	0	4

Values are mean ± SD, or numbers, as appropriate.

Four patients in group II had a urine production below 30 ml/hr, which was an exclusion criterion in group I. The mean urine production tended to be lower in group II in comparison with group I, but the difference was not significant. There were no maternal complications associated with the introduction or maintenance of the radial artery and the Swan-Ganz catheters. An ultrasound diagnosis of severe fetal growth retardation was made in eight patients in group I and in seven in group II.

Baseline hemodynamic measurements

The hemodynamic variables determined before the start of treatment were not statistically different between groups (Table 5.2). Both groups of patients showed cardiac indexes that were markedly reduced and systemic vascular resistances that were elevated compared with the hemodynamic values in normotensive pregnant women (Chapter 3).

Vasodilatation followed by volume expansion (Group I)

The median administered dose of dihydralazine was 2 mg/hr (range 1-3 mg/hr). Fig. 5.1. shows the relative hemodynamic changes after dihydralazine infusion. Mean intra-arterial pressure decreased from 129 to 114 mm Hg, PCWP decreased from 9 to 6 mm Hg and systemic vascular resistance index (SVRI) decreased from 3170 to 2256 dyne.sec.cm^{-5}.m^2; all changes were statistically significant. No significant effect on right atrial pressure was observed. Cardiac index showed a significant rise from 3.3 to 4.1 l.min^{-1}.m^{-2} due to a significant increase in heart rate from 72 to 88 beats.min^{-1}, whereas no significant effect on stroke volume index was observed (Fig. 5.1.). Urine output showed a significant fall; nine patients became oliguric, with a urine output of less than 30 ml/hr. Simultaneously with the drop in PCWP and urine production, the previously normal cardiotocogram showed decreased variability and late decelerations as signs of fetal distress in seven cases, four of which had an ultrasound diagnosis of severe fetal growth retardation. Because of the adverse reactions, the administration of dihydralazine was reduced in two and temporarily stopped in six patients.

The amount of plasma expander administered in the second part of the protocol varied between 250 and 2500 ml, with a median of 1000 ml. The maximum hemodynamic changes obtained after plasma volume expansion are summarized in Table

5.2. and shown in Fig. 5.1. Infusion of plasma restored PCWP to a mean value of 10 mm Hg, but no effect on right atrial pressure was apparent. Cardiac index showed a further increase, mainly due to a further significant rise in heart rate and a small, non-

Table 5.2. Hemodynamic values of preeclamptic patients in both groups, before and after treatment.

	Before treatment			After treatment		
	Group I (n=19)	P	Group II (n=19)	Group I (n=19)	P	Group II (n=19)
Systemic circulation						
Heart rate (beats.min^{-1})	72±10.8	NS	79±9.5	107±11.9*	NS	102±13.9**
Mean intra-arterial pressure (mm Hg)	129±11.5	NS	127±9.4	112±9.8*	NS	107±11.1**
Cardiac index (l.min^{-1}.m^{-2})	3.3±0.68	NS	3.2±0.59	5.2±1.14*	NS	5.3±0.89**
Stroke volume index (ml.beat^{-1}.m^{-2})	46±9.7	NS	41±8.5	49±9.8	NS	52±9.6**
Systemic vascular resistance index (dyn.sec.cm^{-5}.m^{2})	3170±640	NS	3244±690	1727±533*	NS	1624±362**
Left ventricular stroke work index (J.beat^{-1}.m^{-2})	0.73±0.18	NS	0.67±0.14	0.66±0.13	NS	0.68±0.15
Pulmonary circulation						
Mean pulmonary arterial pressure (mm Hg)	15±3.4	NS	11±3.7	19±5.9*	NS	18±5.5**
Pulmonary capillary wedge pressure (mm Hg)	9±3.9	NS	5±3.1	10±4.7	NS	9±4.7**
Right atrial pressure (mm Hg)	4±2.4	NS	1±2.4	5±4.0	NS	3±2.6**
Pulmonary vascular resistance index (dyne.sec.cm^{-5}.m^{2})	146±85	NS	156±50	141±90	NS	130±46
Right ventricular stroke work index (J.beat^{-1}.m^{-2})	0.07±0.02	NS	0.05±0.02	0.08±0.04*	NS	0.10±0.04**

Values are mean (± SD).

* P < 0.01 versus group I before treatment
** P < 0.01 versus group II before treatment
NS = not significant

significant increase in stroke volume. The SVRI fell progressively to a mean of 1727 dyne.sec.cm^{-5}.m^{2}. Urine production improved and the cardiotocographic signs of fetal distress disappeared in all cases.

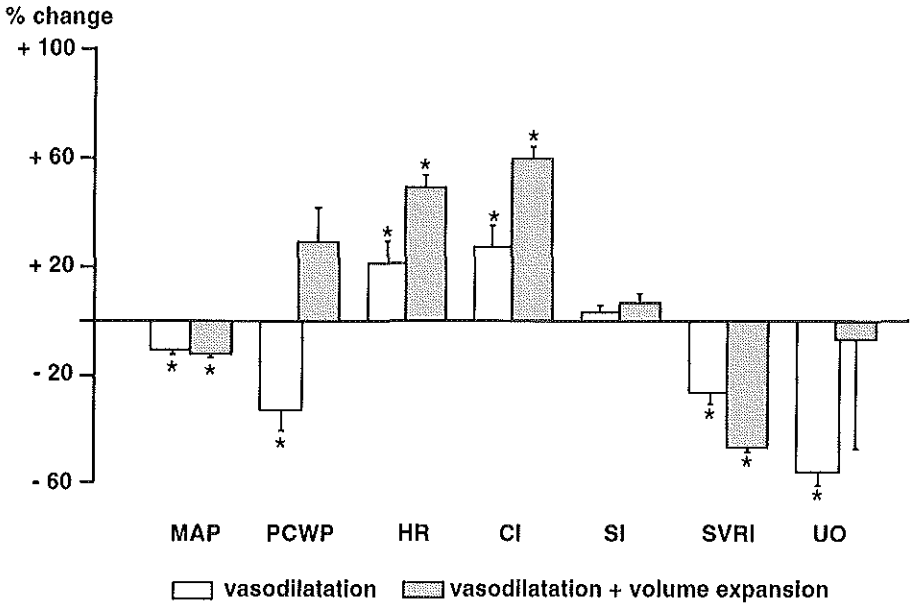
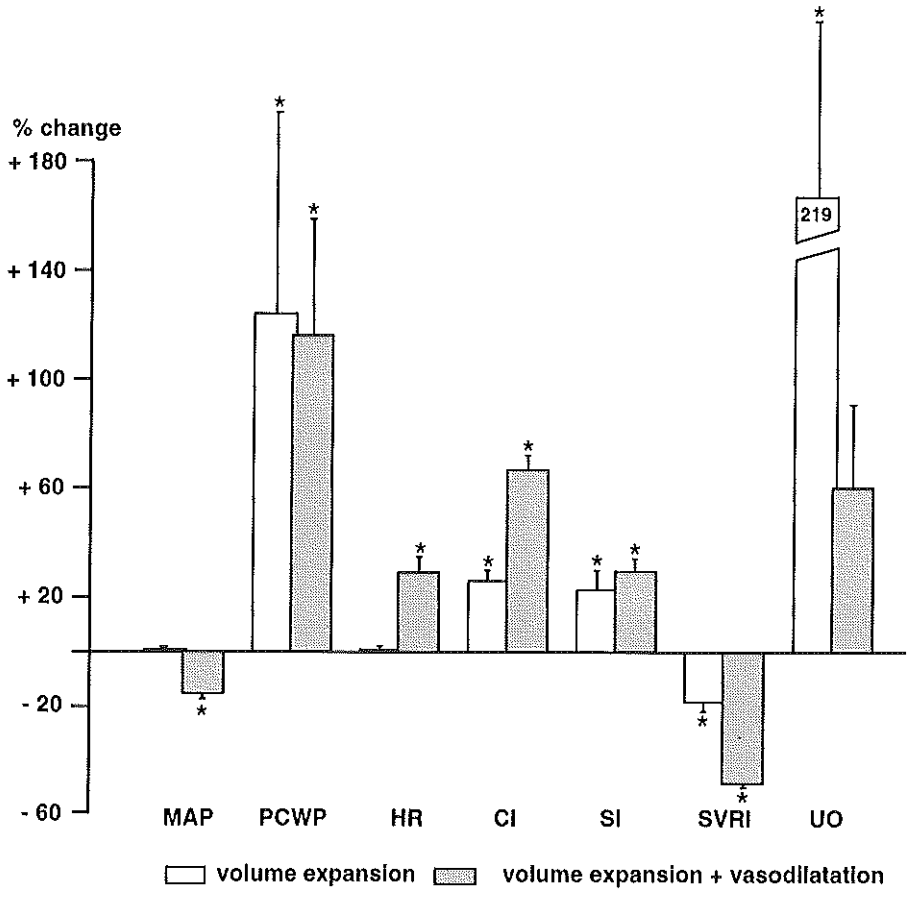


Fig. 5.1. *The mean maximum (SEM) change (%) in hemodynamic values obtained in group I after vasodilatation (open bars) and after vasodilatation followed by volume expansion (solid bars). MAP = Mean intra-arterial pressure; PCWP = Pulmonary capillary wedge pressure; HR = Heart rate; CI = Cardiac index; SI = Stroke volume index; SVRI = Systemic vascular resistance index; UO = Urine output.*
** $P<0.01$, versus untreated.*

Volume expansion followed by vasodilatation (group II)

The total amount of plasma expander administered in the first part of the protocol in group II varied between 250 and 1750 ml, with a median of 750 ml. The hemodynamic changes observed after plasma volume expansion are shown in Fig 5.2. No effect on mean arterial pressure was observed, but plasma infusion was accompanied by a significant rise in PCWP (from 5 to 10 mm Hg), right atrial pressure (from 1 to 3 mm Hg) and cardiac index (from 3.2 to 4.0 $l.min^{-1}.m^{-2}$). The rise in cardiac index was caused by a significant increase in stroke volume index from 41 to 50 $ml.beat^{-1}.m^2$, without any change in heart rate. The SVRI decreased significantly from 3244 to 2670 $dyne.sec.cm^{-5}.m^2$. Urine production increased and no fetal distress was observed. Volume expansion was followed by infusion of dihydralazine at a median rate of 1.5,

with a range of 1-3 mg/hr, resulting in a significant fall in mean arterial pressure of 20 mm Hg. Dihydralazine administration was combined with further plasma volume expansion to a median of 750 (range 250-1750) ml to keep PCWP values around 10 mm Hg.



Legend to Fig. 5.2. *The mean maximum (SEM) change (%) in hemodynamic values obtained in group II after volume expansion (open bars) and after volume expansion followed by vasodilatation (solid bars).*
MAP = Mean intra-arterial pressure; PCWP = Pulmonary capillary wedge pressure; HR = Heart rate; CI = Cardiac index; SI = Stroke volume index; SVRI = Systemic vascular resistance index; UO = Urine output.
** $P<0.01$, versus untreated.*

The cardiac index showed a further rise, accompanied by a significant increase in heart rate, but only a small rise in stroke volume. The SVRI fell significantly to reach a normal value of 1624 dyne.sec.cm^{-5}.m^2 (Fig. 5.2., Table 5.2.). Urine production decreased, but it never fell below pretreatment levels (Fig. 5.2.). Fetal distress occurred in one patient following dihydralazine infusion and necessitated cesarean section.

5.4. Discussion

Central hemodynamics in untreated preeclamptic patients appear to be characterized by low to normal filling pressures, a low cardiac output and a high systemic vascular resistance, as discussed in Chapter 4. These features were also observed in the patients of both groups in the present study.

A reduced circulating volume may induce a secondary increase in systemic vascular resistance and may also be reflected in a low urine production. Indeed, four women were oliguric and for that reason were included in group II to receive plasma volume expansion before treatment with dihydralazine. However, mean urine production and PCWP values were not statistically different between groups.

The results obtained in group I demonstrate that administration of dihydralazine not only produces the desired arteriolar vasodilatation and reduction of cardiac afterload, but that it also results in an undesirable and marked decrease in cardiac preload. It may be presumed that the pronounced dilatation of the arterioles in addition to some venous dilatation, causes marked reduction of the degree of filling of the circulatory system in these relatively hypovolemic patients, leading to a reduced mean circulatory filling pressure.

Following infusion of dihydralazine, a 22 percent increase in heart rate was observed, but circulatory reflexes apparently could not always compensate fully for the fall in venous return to the heart, and clinical signs of circulatory decompensation occurred as indicated by oliguria and fetal distress, most likely due to a reduction in uteroplacental blood flow. Similar hemodynamic effects were observed by others in preeclamptic patients treated with dihydralazine[233], nitroglycerin[38] and diazoxide[166], as well as in pregnant sheep with renal hypertension receiving diazoxide[231]. These effects were reversed by expansion of the circulating volume and an increase in cardiac preload. The disappearance of the cardiotocographic signs of fetal distress after plasma

volume expansion in group I supports findings reported in the literature indicating that plasma volume expansion may improve uteroplacental perfusion[103].

In group I fetal distress occurred after dihydralazine infusion in 50 percent of the growth-retarded fetuses, but in only 27 percent of fetuses with adequate fetal growth as assessed by ultrasound. This supports earlier observations that hypertensive patients with fetal growth-retardation due to an insufficient uteroplacental circulation are prone to develop fetal distress during antihypertensive treatment with (di)hydralazine[213,225].

In the patients of group II plasma volume expansion increased PCWP by 124 percent, but RAP by only 21 percent, indicating a blunted response of RAP to volume expansion. Others did not observe any effect of volume expansion on central venous pressure[11,12,38]. It appears that in pregnant women the PCWP is a more sensitive indicator of left ventricular filling than is central venous pressure, most likely because the right atrium in pregnancy is quite flaccid and accomodates marked increases in volume without an increase in pressure[36,233].

If hypovolemia leads to a compensatory increase in systemic vascular resistance, plasma volume expansion may be expected to cause a fall in mean arterial pressure. Such an effect was indeed observed with large and rapid volume increments[235], but not in most studies using slow and limited plasma volume expansion[11,12,38,83], with one notable exception[74]. In the present study, plasma volume expansion alone appeared to reduce SVRI and to increase cardiac index, but no effect on mean arterial pressure was apparent, and additional administration of the vasodilator dihydralazine was necessary in all cases to obtain vascular resistances comparable with those in normotensive pregnant women (Chapter 3).

In conclusion, our observations indicate that the pregnant woman with severe preeclampsia is not able to cope with a circulatory volume necessary to maintain a cardiac index and a left ventricular filling pressure that is considered physiological in normotensive pregnancy. Vasodilating agents used in the management of severe preeclampsia increase vascular space, thus inducing a further reduction of the already diminished circulatory filling pressure. Depending on the severity of the relative hypovolemic state, compensatory mechanisms may fall short resulting in insufficient perfusion of maternal organs, including the kidney and the uteroplacental unit. These adverse effects of hypotensive therapy can be avoided by expanding circulating volume.

By combining vasodilatation with dihydralazine with plasma volume expansion a hemodynamic state can be obtained in preeclamptic patients that is physiological for pregnancy. However, uncontrolled volume expansion carries a risk of pulmonary edema and cardiac failure[15,171,201]. For that reason volume expansion should not be applied without monitoring pulmonary pressures, for which the use of the pulmonary artery catheter is a prerequisite. In a population of young pregnant women the risks of insertion and maintenance of a Swan-Ganz catheter are small in experienced hands[232] and are fully compensated for by the security gained in the unstable and potentially dangerous hemodynamic situation presented by pregnant patients with severe preeclampsia.

Chapter 6

MATERNAL AND PERINATAL OUTCOME OF TEMPORIZING MANAGEMENT IN 254 CONSECUTIVE PATIENTS WITH SEVERE PREECLAMPSIA REMOTE FROM TERM*

6.1. Introduction

Preeclampsia complicates around 5 percent of all pregnancies and is directly or indirectly responsible for a large proportion of maternal and perinatal mortality and morbidity[228]. Although the cause of preeclampsia is still unknown, the placenta is considered a key factor[181]. Therefore, delivery of fetus and placenta is the only effective treatment, which may benefit the mother but is often not in the interest of the second patient, the fetus, in particular remote from term. The decision to deliver must depend on the estimated balance of maternal and fetal-neonatal risks. In preterm pregnancy complicated by mild preeclampsia the balance of maternal and neonatal interests will usually lead to conservative management, in an attempt to postpone delivery in order to reduce neonatal morbidity and mortality[120,191]. On the other hand, in cases of severe preeclampsia or eclampsia most guidelines recommend expeditious delivery regardless of gestational age[120,209], in particular when preeclampsia is complicated by the HELLP syndrome[209,236]. In recent years, as methods for monitoring maternal and fetal wellbeing improved, these guidelines have been challenged and attempts have been made to postpone delivery also in women with severe preeclampsia remote from term[162,191,207]. However, recent reports of small series of patients suggest that such an approach could be associated with increased maternal morbidity[162].

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In 1985 a protocol of temporizing management of severe preeclampsia remote from term was instituted in our department. The protocol is based on correction of the maternal circulation with plasma volume expansion and pharmacologic vasodilatation under central hemodynamic monitoring[233]. The purpose of this study is to assess the maternal and perinatal outcomes of 254 consecutive patients with severe preeclampsia before 32 weeks gestation managed according to this protocol.

6.2. Subjects and methods

Selection of patients

The study population consisted of all women with severe preeclampsia between 20 and 31 completed weeks of gestation, not in labor and with a live, single fetus, admitted to the antenatal wards of the University Hospital Rotterdam (AZR) between January 1, 1985 and December 31, 1993. The AZR serves as a perinatal tertiary care center for an area with approximately 35.000 deliveries per year.

Severe preeclampsia was defined as the occurrence after 20 weeks' gestation of a diastolic blood pressure, before treatment, of 110 mm Hg or more (Korotkoff 4) and proteinuria of 0.3 g/l or more in a 24 hour urine collection, or the occurrence of repetitive diastolic blood pressure values of 90 mm Hg or more and proteinuria in combination with the HELLP syndrome or eclampsia. The HELLP syndrome was defined as the simultaneous occurrence of a platelet count of less than $100x10^9/l$, serum aspartate aminotransferase (ASAT) and serum alanine aminotransferase (ALAT) concentrations greater than 30 U/l (2 SD above the mean in our hospital), and hemolysis defined by abnormal peripheral smear. Patients with known vascular, renal, hepatic or hematologic disease were excluded. Gestational age was based on the last menstrual period and confirmed by early ultrasound in the majority of cases.

Management protocol

Hemodynamic measurements

All patients were managed with the intention to prolong gestation in order to enhance fetal maturity. Temporizing treatment consisted of bed rest and correction of

the maternal circulation to previously established normal hemodynamic values for the second half of gestation (Chapter 3) by means of pharmacologic vasodilatation and plasma volume expansion under central hemodynamic monitoring. A baseline electrocardiogram was recorded in each patient, followed by pulmonary artery catheterization and radial arterial line placement in the obstetric intensive care unit as described in detail in Chapter 2. Baseline values of systemic and pulmonary arterial and venous pressures, and of cardiac output, were obtained after a stabilization period of approximately one hour after catheterization. Cardiac output was measured in triplicate in supine position at end-expiration by means of thermodilution, as described in Chapter 2.

Hemodynamic treatment

Patients with a pulmonary capillary wedge pressure (PCWP) of less than 10 mm Hg received an intravenous infusion of pasteurized plasma at a rate of approximately 250 ml/hr to reach and maintain PCWP values of 10-12 mm Hg. If, after volume expansion, the cardiac index was still less than 3.5 $l.min^{-1}.m^{-2}$ and the systemic vascular resistance index was more than 2000 $dyn.s.cm^{-5}.m^2$, patients received an intravenous infusion of dihydralazine at a rate of 1 mg/hr followed by hourly increments of 1 mg, until the cardiac index had reached a value between 3.5 and 4.6 $l.min^{-1}.m^{-2}$ and a systemic vascular resistance index of 2000 $dyn.s.cm^{-5}.m^2$ or less had been obtained. When cardiac index and systemic vascular resistance had reached normal values but diastolic blood pressure was still 100 mm Hg or more, antihypertensive treatment with alpha-methyldopa was added. After a stable hemodynamic condition had been obtained and maintained for 1-2 days, the vascular catheters were removed and the patient was transferred to the antenatal ward. Antihypertensive treatment was continued under close monitoring of blood pressure, fluid balance, and laboratory values.

Clinical management

All patients kept bed rest and received an unrestricted diet. Maternal condition was assessed by monitoring blood pressures, fluid balance and pertinent laboratory values including protein in 24-hour urine samples, complete blood counts, liver enzymes (ASAT, ALAT, gamma glutamyl transferase, serum lactic dehydrogenase) and total

bilirubin, renal function tests (serum creatinine and uric acid) and tests for hemolysis (peripheral blood smear, serum haptoglobin). Coagulation tests (activated partial thromboplastin time, prothrombin time, normotest, thrombotest, fibrinogen, fibrinogen degradation products, antithrombin III) were done on admission in the majority of patients, and during treatment when indicated. Anticonvulsant treatment with intravenous diazepam was used in eclamptic patients and when eclampsia appeared to be imminent, as judged by hyperactive deep tendon reflexes with clonus. Platelet transfusions were given at the time of cesarean section when platelet counts were $30x10^9/l$ or less. Ultrasound examination was performed in all patients to detect fetal growth retardation and congenital abnormalities. Fetal condition was assessed by cardiotocography (nonstress CTG) on admission and at least daily thereafter. If labor occurred and delivery was still to be postponed, uterine activity was inhibited using intravenous fenoterol. Corticosteroids to accelerate fetal lung maturation were not used in patients with preeclampsia during the period of the study.

The decision to deliver was taken by the attending obstetrician in consultation with the neonatologist, weighing combined maternal and fetal risk against the risks of neonatal mortality and morbidity. The mode of delivery was determined by fetal condition. Neonates requiring intensive care were transferred to our neonatal intensive care unit. Pulmonary surfactant therapy was used after 1991.

End points of study

The study protocol was approved by the University and Hospital Ethics Committee. The primary end points of the study were the number of days of prolongation of gestation after admission, predefined maternal antepartum and postpartum complications (mortality, HELLP-syndrome, eclampsia, abruptio placentae, postpartum hemorrhage, pulmonary edema) and specified measures of fetal and neonatal outcome (birthweight, perinatal mortality, neonatal morbidity as judged by Apgar score, artificial ventilation, bronchopulmonary dysplasia, cerebral bleeding).

Birthweight is presented as actual weight at birth and related to the Dutch reference curve, corrected for gestational age, parity and fetal sex[107]. Data on perinatal mortality comprise all stillbirths and neonatal deaths occurring within 28 days of birth; infant mortality includes all deaths between 28 days and one year after birth.

Bronchopulmonary dysplasia is defined as a requirement for oxygen at 28 days of life, irrespective of gestational age at birth.

Data analysis

Data analysis was based on intention to treat and included all patients, also when they were delivered before the actual start of temporizing treatment. Data are presented as median (range) unless stated otherwise. Hemodynamic and laboratory values were examined by nonparametric oneway analysis of variance for repeated measurements and Wilcoxon's rank sign test as appropriate. Categorical variables were assessed with the χ^2-test. A p-value of less than 0.05 (two-tailed) was considered significant.

6.3. Results

Clinical characteristics

During the period of the study 254 patients with severe preeclampsia before 32 weeks' gestation who met the inclusion criteria were delivered at this center. Clinical characteristics on admission are summarized in Table 6.1. The majority of the patients

Table 6.1. *Clinical characteristics on admission of 254 patients with severe preeclampsia.*

Age (yrs)	27 (18-44)
Nulliparous	188 (74%)
Gestational age (wks)	29.3 (21.7-31.9)
Diastolic blood pressure (mm Hg)	110 (90-170)
Antihypertensive treatment before admission	138 (54.3%)
Eclampsia before admission	12 (4.7%)
HELLP before admission	85 (33.5%)
Upper abdominal pain	116 (45.7%)
Severe fetal growth retardation	50 (19.7%)

Values are median (range), or numbers (percentage), as appropriate.

(94 percent) were referred from regional hospitals, usually because of complications such as the HELLP syndrome (33 percent), eclampsia (5 percent), or severe fetal

growth retardation (20 percent); half the number of patients had already received antihypertensive treatment because of a diastolic blood pressure of 110 mm Hg or more.

Baseline hemodynamic measurements showed patterns as described in Chapter 4, with generally low cardiac indexes and high systemic vascular resistances in untreated patients, and an extremely variable pattern in patients who had already been treated. The total amount of plasma expander administered during treatment varied between 1-4 liters, mainly administered during the first three days after admission. All patients received dihydralazine in doses varying between 1-15 mg/hr; 40 percent of the patients also required alpha-methyldopa in doses between 750 mg and 4 g/24h. The relevant laboratory data on admission are shown in Table 6.2. During treatment proteinuria increased significantly ($p<0.001$) from a median value of 2.8 g/l to 4.9 g/l, without changes in plasma creatinine levels. None of the patients developed a creatinine level above 200 μmol/l. Between admission and delivery the hemoglobin concentration showed a significant fall from 7.7 to 7.0 mmol/l ($p<0.001$).

Table 6.2. *Laboratory data on admission.*

Proteinuria	(g/l)	2.8 (0.3-35.9)
≥ 5 g/l		80
Creatinine	(μmol/l)	72 (40-165)
Uric acid	(mmol/l)	0.41 (0.16-0.84)
Hemoglobin	(mmol/l)	7.7 (4.9-10.7)
Hematocrit	(l/l)	0.37 (0.23-0.51)
Platelets	($x10^9$/l)	145 (14-436)
50-100		73
< 50		22
Bilirubin	(μmol/l)	8 (2-75)
ASAT	(U/l)	27 (7-779)
ALAT	(U/l)	20 (3-780)
LDH	(U/l)	356 (168-3219)
Haptoglobin	(g/l)	0.2 (<0.1-2.8)

Values are median (range), or numbers, as appropriate.

Maternal outcome

Table 6.3. summarizes maternal outcome. There were no maternal complications associated with the introduction or maintenance of the radial artery or Swan-Ganz

catheter. Pregnancy was terminated within 48 hours after admission in 13 percent of patients because of fetal distress as judged by the nonstress fetal CTG (n=29), or fetal death (n=3). When patients delivered within 48 hours are omitted from the calculation, the median prolongation of pregnancy was 17 days with a prolongation of 14 days or more in 51 percent of the patients.

Table 6.3. *Maternal outcome.*

Prolongation of pregnancy (days)	14 (0-62)
Termination within 48 hrs	32 (12.6%)
Prolongation in remaining patients (days)	17 (3-62)
Antepartum resolution of HELLP	48 (45.7%)
Prolongation of pregnancy (days)	22 (8-62)
Maternal mortality	0
Maternal morbidity	
Eclampsia	1
Visual disturbances	3
Abruptio placentae	
complete	1
partial	12
Hemorrhagic problems	15
HELLP syndrome	
antepartum	20
postpartum	4
Pulmonary edema	4
Termination of pregnancy	
Vaginal delivery	43 (16.9%)
spontaneous labor	9
induced labor	34
Cesarean section	211 (83.1%)
fetal indication	181
maternal indication	22
combined indication	8

Values are median (range), or numbers (percentage), as appropriate.

Eclampsia occurred in one patient shortly after admission, before the start of treatment, followed by cortical blindness; normal vision returned one day after cesarean section for fetal distress. Visual disturbances were observed in two other patients. One severely hypertensive patient developed cortical blindness one day after the start of treatment; normal vision returned within two days, and pregnancy was prolonged by six days. In the second patient temporary visual problems after delivery were due to retinal edema. Bleeding problems, observed in 6 percent of patients, were not severe and consisted of abdominal hematoma following cesarean section (n=12), postpartum uterine bleeding (n=1), hematemesis (n=1) and a hematoma of the vulva (n=1). Renal failure or disseminated coagulopathy was not observed.

In all patients with the HELLP syndrome the upper abdominal pain abated and usually disappeared within 2-3 hours after the start of treatment. In 42 of 75 patients who were admitted with HELLP and who were not delivered within 48 hours because of fetal distress, all signs and symptoms disappeared before delivery. On the other hand, 20 women developed a complete antepartum HELLP syndrome during treatment, which resolved in six patients before delivery. All four patients with pulmonary edema were admitted with the HELLP syndrome. Two women developed antepartum pulmonary edema; the first one during induction of labor with prostaglandin E_2 after fetal death, the second one during tocolysis with fenoterol. Both patients were treated successfully with diuretics. In the two patients with pulmonary edema after delivery a diagnosis of cardiomyopathy was made by ultrasound; one of these patients had received prostaglandin E_2 after delivery. Both patients needed artificial ventilation for 2-3 days and recovered completely.

Perinatal outcome is shown in Table 6.4. The high proportion of very small-for-

Table 6.4. *Perinatal and neonatal outcome.*

Gestational age at delivery (wks)	31.2 (22.3-37.7)
Birthweight (g)	1102 (180-2370)
Below 10th percentile	149 (58.7%)
Below 2.3rd percentile	37 (14.6%)
Perinatal mortality	52 (20.5%)
Fetal deaths	31
gestational age (wks)	27.1 (22.3-34.4)
birthweight (g)	680 (180-2370)
Neonatal deaths	21
gestational age (wks)	30.0 (26.6-33.7)
birthweight (g)	990 (480-1510)
Infant deaths	8
Primary cause of neonatal death	
Respiratory insufficiency	16
Sepsis	3
Ruptured cerebral aneurysm	1
Lethal congenital abnormality	1
Neonatal morbidity	
Apgar score at 5 min < 7	25
Platelet count < $100x10^9/l$	30
Cerebral bleeding	
grade I-II	8
grade III	2
Artificial ventilation	115
duration (days)	5 (0.1-61)
Bronchopulmonary dysplasia	25

Values are median (range), or numbers (percentage), as appropriate.

gestational age (<2.3rd percentile) infants is mainly caused by the 73 women admitted at a gestational age of 27 weeks or less, of whom 25 percent were delivered of very small-for-gestational age infants compared with 10.5 percent in women admitted between 27 and 32 weeks' gestation ($p<0.01$). Total perinatal loss was 20.5 percent, with a 95 percent confidence interval of 15-26 percent. Of the 52 cases of perinatal loss, 60 percent were due to fetal death.

All stillbirths, except one caused by abruptio placentae at 34 weeks' gestation, occurred in cases with severe fetal growth retardation at gestational ages below 30 weeks. Although fetal distress was recognized it was decided not to deliver because of low estimated birhtweight, small chance of survival, or high estimated risk of serious morbidity and later handicap. The majority of neonatal deaths (76 percent) were due to respiratory distress associated with very preterm birth. One of the two infants with a cerebral bleeding grade III had a ruptured cerebral aneurysm and died one day after birth, the other infant survived and showed a minor delay in speech development at the age of 1 year. No correlation could be demonstrated between the last maternal platelet count before delivery and neonatal platelet count. Eight infants died in their first year of life, in all cases due to severe bronchopulmonary dysplasia.

Table 6.5. shows perinatal outcome related to gestational age on admission and

Table 6.5. *Perinatal outcome by gestational age on admission.*

Gestational age (wks)	Number	Prolongation (days)	Birthweight (g)	Birthweight percentile < 10th (n)	Birthweight percentile < 2.3rd (n)	Fetal deaths (n)	Neonatal deaths (n)	Perinatal mortality %	95%CI*
<26	25	16 (2-42)	650 (180-990)	16	9	16	5	84	64-95
26	18	15 (0-60)	900 (480-1785)	11	3	5	3	44	22-69
27	30	18 (3-61)	1027 (675-1800)	22	6	5	4	30	15-49
28	42	12 (0-62)	965 (640-2130)	25	4	1	6	17	7-31
29	44	13 (0-46)	1115 (625-2140)	27	8	3	1	9	3-22
30	47	12 (1-50)	1290 (610-1860)	25	2	0	2	4	1-15
31	48	13 (0-39)	1527 (955-2370)	23	5	1	0	2	1-11

*CI : 95% confidence interval

Values are median (range), or numbers, as appropriate.

prolongation of pregnancy. Of the 25 pregnancies with an onset of preeclampsia before 26 weeks' gestation, only four babies survived and did well, after a median prolongation of pregnancy of 16 (2-42) days. Perinatal survival improved significantly with gestational age, with reductions in perinatal mortality of approximately 50 percent per week between 27 and 32 weeks' gestation on admission.

6.4. Discussion

Severe preeclampsia below 32 weeks' gestation is an infrequent complication of pregnancy and published experience in managing such patients is limited. In this report we present our experience with temporizing management in what is to the best of our knowledge the largest consecutive series of patients with severe preeclampsia remote from term treated in one center. Our treatment is based on the assumption that symptomatic correction of maternal hemodynamics may improve perfusion of maternal tissues and organs and could thus benefit the mother and perhaps also the fetus[103,233]. Whereas hemodynamics in untreated preeclamptic women are characterized by a reduced cardiac output and circulating volume and a high peripheral vascular resistance, patients receiving antihypertensive drugs and intravenous fluids show hemodynamic patterns that are variable and unpredictable (Chapter 4). For that reason we consider central hemodynamic monitoring an indispensable tool to assess the hemodynamic balance of flow, pressure and resistance in the systemic and in particular the pulmonary circulations in treated preeclamptic patients referred from other hospitals, and to monitor antihypertensive treatment and plasma volume expansion[233]. The maternal risks of the invasive hemodynamic monitoring applied in the first 1-3 days of treatment appear to be small in our hands. This may, at least in part, be attributed to the small number of skilled operators involved, and to the presence in the obstetric intensive care unit of an experienced medical and nursing staff, 24 hours per day and 7 days per week.

In contrast to other reports on conservative management in which patients with the HELLP syndrome[160,161,162,206,207], with eclampsia[149,160,162,206,207,209] with severe fetal growth retardation[206,207], and with fetal distress[160,161,206,207] were excluded, our study includes all patients with early onset preeclampsia and a live fetus on admission. Despite the presence of eclampsia, HELLP, and fetal compromise in more than 40

percent of cases, the mean prolongation of pregnancy of 16 (range 0-62) days is similar[139,161,206,207,209], or better[91,149,160,162] than that reported in comparable studies in selected patients.

In contrast to the results of a recent study[162] suggesting that expectant management without hemodynamic correction in patients with severe pre-eclampsia may increase maternal morbidity, hemodynamic treatment was associated in our study with marked objective and subjective improvement in maternal condition. We did not observe maternal mortality[149,208] or severe complications such as ruptured liver hematoma[208,209], intracerebral hemorrhage[209] and renal failure[149,162,208,209]. In our study four (1.6 percent) patients developed pulmonary edema, which compares favorably with the reported incidence of 2.9 percent among preeclamptic patients[201]. Two of these patients were treated with prostaglandin E_2, and one with fenoterol, drugs that have been reported to cause[85] or exacerbate pulmonary edema[119]. The observation of complete resolution of the HELLP syndrome before delivery in 51 percent of the patients in whom pregnancy could be prolonged for more than 48 hrs, is in contrast with the generally held view that HELLP invariably runs a progressive course and should be treated by immediate delivery[242]. Although it is also said that the natural history of the HELLP syndrome is that of a deteriorating postpartum process[132], HELLP recurred post partum in only two patients. A further assessment of the results of temporizing management of preeclamptic patients with the HELLP syndrome is presented in Chapter 7 of this thesis.

The rise in protein excretion observed in the majority of the preeclamptic patients during temporizing treatment may be due to the plasma volume expansion, which is known to magnify proteinuria in patients with the nephrotic syndrome[199].

As shown in Table 6.5., a gain in pregnancy of one week appears to improve perinatal outcome considerably in pregnancies with a gestational age below 32 weeks , which agrees with previous studies[184,239]. However, assessment of the perinatal results of prolongation of pregnancy in our observational study is hampered by the absence of an appropriate control group, and comparison with the perinatal results of expectant management in preeclamptic patients reported in the literature is difficult because gestational age on admission is often not comparable[91,139,160,161,165,206,209]. In addition, in many reports patients are excluded for various reasons, including fetal growth retardation and fetal distress[139,149,160,161,162,206,207,209]. Finally, because of recent advances

in perinatal care results obtained in recent years cannot be compared with those of earlier studies. Two studies[162,207] on expectant management in preeclamptic patients with a mean gestational age on admission that is comparable with our study are summarized in Table 6.6.

Table 6.6. *Comparison between maternal and perinatal outcome of temporizing management in patients with severe preeclampsia remote from term in the University Hospital Rotterdam (AZR) 1985-1993, and as published in the literature.*

	This study n=254	Oláh et al. 1993[162] n=28	Sibai et al. 1994[207] n=49
Gestational age on admission (wks)	28.9 (21-31)	29.2 (24-32)	30.7 (28-32)
Platelets < $100x10^9$/l before admission	95 (37.4%)	0	0
HELLP before admission	85 (33.5%)	0	0
Eclampsia before admission	12 (4.7%)	0	0
Fetal exclusion criteria	-	+	+
Prolongation of pregnancy (days)	16.2 (0-62)	9.5 (2-26)	15.4 (4-36)
Maternal mortality	0	0	0
Gestational age at delivery (wks)	31.2±2.6	30.6±4.7	32.9±1.5
Birthweight (g)	1160±390	1480±450	1622±360
Below 10th percentile	149 (58.7%)	?	15 (30.1%)
Perinatal mortality (%)	20.5	7.1	0
Fetal deaths	31	0	0
Neonatal deaths	21	2	0

Values are mean ± SD (range), or numbers (percentage), as appropriate.

Oláh et al.[162] reported a perinatal mortality of only 7.1 percent in a retrospective analysis of 28 selected patients with severe preeclampsia in whom pregnancy was prolonged by 9.5 days. In that study patients were treated with nifedipine and methyldopa and were only selected for conservative treatment if hypertension could be satisfactorily controlled. Only patients without an unspecified maternal or fetal indication for immediate delivery were included. Sibai et al.[207] reported a randomized trial of agressive (n=46) versus expectant (n=49) management in preeclamptic patients between 28 and 32 weeks gestation. Expectant management was begun after a stable maternal condition was obtained during a 24-hour observation period using magnesium sulfate, hydralazine or nifedipine. In that study no perinatal mortality occurred in both groups, but patients with fetal growth retardation and fetal distress were excluded. In the study by Sibai et al.[207] as well as in the study of Oláh et al.[162] corticosteroids to

accelerate fetal lung maturation were used, which may be an important advantage of prolongation of pregnancy for at least 48 hours[42]. During the study period corticosteroïds were not used in patients with preeclampsia in our center, which may have had a negative effect on the incidence and severity of the neonatal respiratory distress syndrome. Our reluctance to administer corticosteroids to hypertensive patients was based on the results of the first randomized trial of antenatal corticosteroid therapy[41]. That trial included 90 preeclamptic women, and 12 fetal deaths were observed in 47 treated patients compared with three fetal deaths among 43 nontreated patients. Later observational studies, although small, have failed to confirm an excess risk of fetal death associated with the use of antenatal corticosteroids in hypertensive patients and because of convincing evidence of its efficacy in the prevention of the neonatal respiratory distress syndrome[41], antenatal corticosteroid therapy was introduced in the management of preeclamptic patients in our department in 1994. The perinatal mortality of 20.5 percent in our patients compares favorably with that of 62 percent in the 50 patients reported by Moodley et al.[149], in which study patients with impending or evident eclampsia were excluded. Also in this study corticosteroids were used. The study of Moodley et al.[149] is omitted from Table 6.6., because of too many unreported data.

Our study confirms findings of earlier studies that perinatal outcome in patients with an onset of preeclampsia before 26 weeks is generally poor[149,161,165,209] and cannot be markedly improved by prolongation of pregnancy. The high incidence of fetal growth retardation in our study is consistent with earlier reports[122,139,150] and suggests that the fetal-placental impact of severe preeclampsia has preceded overt clinical disease by a considerable period of time.

In conclusion, our experience obtained in a large number of patients with severe early-onset preeclampsia shows that expectant management with plasma volume expansion and pharmacologic vasodilatation under invasive monitoring of the maternal circulation and with careful surveillance of maternal and fetal condition may delay delivery and does not appear to be associated with an increased risk of maternal morbidity and mortality. Such treatment should only be practiced in tertiary care centers with adequate facilities for mother and infant. Controlled studies are needed to further define the value of temporizing hemodynamic treatment in patients with severe early

onset preeclampsia.

Chapter 7

TEMPORIZING MANAGEMENT OF SEVERE PREECLAMPSIA WITH AND WITHOUT THE HELLP SYNDROME*

7.1. Introduction

It has long been recognized that preeclampsia may be associated with hemolysis, elevated liver enzymes, and a low platelet count[24,175], a triad given the acronym of HELLP by Weinstein a decade ago[237]. The incidence of HELLP in women with preeclampsia has been reported to vary between 4-12 percent[208] but depends on the diagnostic criteria used. Patients with HELLP have a high risk of maternal morbidity and mortality[140,175,204,208,237], and the reported perinatal mortality ranges from approximately 8 percent[180,218,236] to as high as 37 percent[208]. As the clinical course of HELLP is considered to be rapidly progressive, and termination of pregnancy is as yet the only treatment that cures preeclampsia, most obstetricians follow Weinstein's recommendation[236] of prompt termination of pregnancy, regardless of gestational age[172,180,208,224]. This view is underscored in a recent American consensus report on high blood pressure in pregnancy[242]. There are a few reports of attempts to prolong gestation in patients with mild HELLP in the late second or early third trimester, but the number of patients treated is too small to compare incidences of important maternal and fetal outcomes[34,90,130,133,218,224].

Since prematurity is the main cause of neonatal mortality and morbidity in patients with severe preeclampsia[80,187], we have tried to prolong pregnancy in order to enhance fetal maturity in all preeclamptic or eclamptic patients with or without HELLP and a gestational age of less than 34 weeks using pharmacologic vasodilatation, plasma volume expansion, and central hemodynamic monitoring under intensive care conditions, as described in Chapter 6 of this thesis. In an attempt to contribute to the

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development of rational guidelines for management we compared the course and outcome of pregnancy in 128 consecutive preeclamptic and eclamptic patients with HELLP with results obtained in 128 patients with equally severe preeclampsia or eclampsia without HELLP, matched for maternal and gestational age. The aim of the study was to test the hypothesis that the clinical course and outcome of pregnancy in patients with severe preeclampsia receiving temporizing hemodynamic treatment does not depend on the presence or absence of HELLP.

7.2. Subjects and methods

Selection of patients

Between January 1, 1985 and December 31, 1993, 371 consecutive patients with a duration of pregnancy of less than 34 weeks, a live fetus and no history of renal, liver, or hematologic disease were admitted to the antenatal wards of the University Hospital Rotterdam (AZR), which serves as the tertiary care center for an area with approximately 35.000 deliveries per year, for temporizing management of severe preeclampsia. Preeclampsia was defined as the occurrence after 20 weeks' gestation of a diastolic blood pressure of 90 mm Hg or more (Korotkoff 4) on two occasions at least 4 hours apart, and proteinuria of 0,3 g/l or more in a 24 hour urine collection period. Of the 371 preeclamptic patients, 129 had HELLP, defined as the simultaneous occurrence of a platelet count of less than $100x10^9$/l, serum aspartate aminotransferase (ASAT) and serum alanine aminotransferase (ALAT) concentrations greater than 30 U/l (2 SD above the mean in our hospital), and hemolysis defined by an abnormal peripheral smear.

Each preeclamptic patient with HELLP was matched for gestational age on admission ($\pm$ 1 wk) with one or more coded patients from the group of 242 pre-eclamptic women without HELLP, but each of these women was matched only once. In case of more than one matching patient for gestational age, the one with the closest matching maternal age ($\pm$ 1 yr) and, finally, with the best match for parity (nulliparous or multiparous) was chosen. The matching procedure was blinded for coded patients, without knowledge of other patient characteristics or outcome of pregnancy.

Management protocol

All patients were managed with the intention to prolong gestation in order to enhance fetal maturity. Treatment consisted of bed rest and correction of the maternal circulation by means of pharmacologic vasodilatation and plasma volume expansion under central hemodynamic monitoring.

Laboratory data obtained on admission and during management included protein in 24-hour urine samples, a complete blood count, liver enzymes (ASAT, ALAT, serum lactic dehydrogenase) and total bilirubin, renal function tests (serum creatinine, uric acid), tests for hemolysis (peripheral blood smear, serum haptoglobin), and coagulation tests (activated partial thromboplastin time, prothrombin time, normotest, thrombotest, fibrinogen, fibrinogen degradation products, antithrombin III). The results of platelet counts and coagulation tests were used to define suspected disseminated intravascular coagulation (DIC) in the presence of two abnormal tests and definitive DIC with three abnormal tests[89].

Hemodynamic measurements

Each patient underwent pulmonary artery catheterization and radial arterial line placement in our obstetric intensive care unit, and hemodynamic measurements were carried out as described in detail in Chapter 2. Baseline hemodynamic values were obtained after a stabilization period of approximately one hour.

Hemodynamic treatment

Patients with a pulmonary capillary wedge pressure (PCWP) of less than 8 to 10 mm Hg and/or a cardiac index below 3.5 $l.min^{-1}.m^{-2}$ received intravenous infusion of pasteurized plasma at a rate of approximately 250 ml/hr to reach and maintain PCWP values of 10 to 12 mm Hg, and a cardiac index between 3.5-4.6 $l.min^{-1}.m^{-2}$. If cardiac index was still less than 3.5 after volume expansion, and diastolic arterial blood pressure was 100 mm Hg or more, patients received an intravenous infusion of dihydralazine at a rate of 1 mg/hr followed by hourly increments of 1 mg, until the cardiac index had reached a value between 3.5 and 4.6 $l.min^{-1}.m^{-2}$, diastolic blood pressure was between 90 and 100 mm Hg, and a systemic vascular resistance index of 2000 $dyn.s.cm^{-5}.m^2$ or less had been obtained. When cardiac index and systemic

vascular resistance had reached normal values but diastolic blood pressure was still 100 mm Hg or more, antihypertensive treatment with alpha-methyldopa was added. After a period of hemodynamic stabilization of 1-2 days, the vascular catheters were removed and management was continued in the antenatal ward with the same regimen under close monitoring of blood pressure, fluid balance, and laboratory values.

Clinical management

Anticonvulsant treatment with intravenous infusion of diazepam was applied in eclamptic patients and in patients in whom eclampsia appeared to be imminent, determined by hyperactive deep tendon reflexes with clonus. Platelet transfusions were given at the time of caesarean section when platelet counts were $30x10^9/l$ or less. Ultrasound examination was performed on all patients to detect fetal growth retardation and congenital abnormalities. Fetal condition was assessed by fetal cardiotocography (nonstress CTG) on admission and at least once daily thereafter. Corticosteroids to accelerate fetal lung maturation were not used in patients with preeclampsia during the period of the study. The decision to deliver the patient was taken by the attending obstetrician in consultation with the neonatologist, weighing combined maternal and fetal risk against the risks of neonatal mortality and morbidity. The mode of delivery was determined by fetal condition. Neonates requiring intensive care were transferred to our neonatal intensive care unit. Pulmonary surfactant therapy was used after 1991.

End points of study

The study was part of a larger prospective investigation on the efficacy of temporizing management of preeclampsia and eclampsia approved by the University and Hospital Ethics Committee, for which informed consent was obtained from all patients. The primary end points of the study were the number of days of prolongation of gestation, predefined maternal antepartum and postpartum complications (mortality, eclampsia, abruptio placentae, postpartum hemorrhage), birthweight, fetal mortality (all fetal deaths, irrespective of birthweight or gestational age), neonatal mortality (within 28 days after birth), and neonatal morbidity (artificial ventilation, bronchopulmonary dysplasia, cerebral bleeding).

Data analysis

Data analysis was based on intention to treat and included all patients selected for the study. Data are presented as median (range) throughout. Measured variables were statistically analyzed using Wilcoxon's rank sum test for comparison between groups, and the rank sign test for comparison within groups. Correlations were assessed with the Spearman test, and categorical data were analyzed with the χ^2-test. A p-value of less than 0.05 (two-tailed) was taken to represent statistical significance.

7.3. Results

Clinical characteristics

Characteristics on admission in both groups are summarized in Table 7.1. The level of diastolic blood pressure was not different between groups. Six patients with and six without HELLP already had been treated for eclampsia before referral. One of the

Table 7.1. *Clinical characteristics on admission.*

	with HELLP (n=128)	without HELLP (n=128)
Age (yrs)	27 (18-45)	28 (18-43)
Nulliparous	100 (78%)	95 (74%)
Gestational age (wks)	30.0 (23-33)	30,0 (23-33)
Diastolic blood pressure (mm Hg)	110 (90-145)	110 (90-150)
Eclampsia before admission	6 (4.7%)	6 (4.7%)
Upper abdominal pain	106 (82.8%)	22 (17.2%)
Referred patients	119 (93%)	106 (82.8%)

Values are median (range), or numbers (percentage), as appropriate.

129 HELLP patients, with a gestational age of 22 weeks on admission, could not be matched and was excluded from the analysis.

Laboratory data

The relevant laboratory data are shown in Table 7.2. On admission all variables defining HELLP were significantly different between groups, but no differences were observed between values of proteinuria, creatinine and uric acid.

Table 7.2. *Laboratory data on admission.*

		with HELLP (n=128)	without HELLP (n=128)	p*
Proteinuria	(g/l)	2.8(0.3-25.6)	2.3(0.3-35.9)	NS
Creatinine	(μmol/l)	69(40-169)	72(42-182)	NS
Uric acid	(mmol/l)	0.41(0.20-0.84)	0.42(0.16-0.62)	NS
Hemoglobin	(mmol/l)	7.4(5.5-9.7)	8.0(5.2-10.2)	<0.001
Platelets	($x10^9$/l)	62(13-99)	195(52-386)	<0.001
50-100		96	5	
< 50		32	0	
ASAT	(U/l)	99(34-2530)	21(10-236)	<0.001
ALAT	(U/l)	100(31-3380)	14(4-259)	<0.001
LDH	(U/l)	583(187-7770)	301(130-1591)	<0.001
Haptoglobin	(g/l)	0.1(0.0-1.6)	0.8(0.0-2.7)	<0.001

* Differences between patients with and without HELLP on admission
NS = not significant; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; LDH = lactic dehydrogenase

Values are median (range), or numbers, as appropriate.

During treatment platelet concentration showed a temporary fall of more than $20x10^9$/l in five patients with HELLP. In 88 of 106 women with HELLP who were not delivered within 48 hours after admission, platelet concentration showed a sustained rise of $20x10^9$/l or more, and a platelet count of $100x10^9$/l or more was obtained before delivery in 78 patients. A significantly greater number of preeclamptic patients with HELLP (60 percent) than without HELLP (14 percent) met the criteria for suspected disseminated intravascular coagulation (DIC), based in all cases on a platelet count below $150x10^9$/l and an antithrombin III activity (AT III) below 80 percent. The results of the other coagulation tests were within normal limits in both groups, and definitive DIC was only observed in three HELLP patients and one patient without HELLP. The number of patients with suspected DIC in the HELLP group decreased significantly ($p < 0.01$) during treatment, mainly due to a rise in platelet count; on the other hand, the number of patients with suspected DIC in preeclamptic women without HELLP increased during treatment ($p < 0.05$) because of a fall in platelet count. Between admission and delivery the hemoglobin concentration showed a significant ($p < 0.001$) fall in both groups. The amount of proteinuria increased in most patients with or

without HELLP, without changes in plasma creatinine levels.

Maternal and perinatal outcomes

Table 7.3 summarizes maternal and perinatal outcomes. A decision to terminate

Table 7.3. *Maternal and perinatal outcomes.*

	with HELLP (n=128)	without HELLP (n=128)
Prolongation of pregnancy (days)	10 (0-62)	14 (0-60)
Termination within 48 hrs	22	17
Prolongation in remaining patients (days)	15 (3-62)	17 (3-60)
Antepartum resolution of HELLP	55	-
Prolongation of pregnancy (days)	21 (7-62)	-
Maternal mortality	0	0
Maternal morbidity		
Placental abruption	5	7
Eclampsia	2	1
Hemorrhagic problems	11	7*
Termination of pregnancy		
Vaginal delivery	26	18
spontaneous labor	12	8
induced labor	14	10
Cesarean section	102	110
fetal indication	87	95
maternal indication	10	12
combined indication	5	3
Gestational age at delivery (wks)	32.1 (25.1-37.7)	32.3 (24.4-37.1)
Birthweight (g)	1200 (360-2655)	1235 (460-2545)
Below 10th percentile	72	75
Below 5th percentile	35	36
Perinatal mortality (%)	14.1	14.8
Fetal deaths	11	11
gestational age (wks)	28.3 (25.1-34.4)	26.9 (24.4-30.0)
birthweight (g)	680 (360-2370)	685 (460-990)
Neonatal deaths	7	8
gestational age (wks)	28.1 (26.6-31.9)	30.3 (28.0-36.6)
birthweight (g)	765 (480-1510)	1060 (840-1625)
Neonatal morbidity		
Platelet count < $100x10^9/l$	13	20
Cerebral bleeding		
grade I-II	2	4
grade III	0	1
Artificial ventilation	57	53
duration (days)	3.5 (0.1-42)	4 (0.5-101)
Late neonatal death > 1 mth	0	1

* $P < 0,05$

Values are median (range), or numbers, as appropriate.

pregnancy within 48 hours after the start of treatment was taken in a similar number of preeclamptic patients with (17 percent) and without (13 percent) HELLP. The indication for delivery in those patients concerned fetal distress as judged by the nonstress fetal CTG in 86 percent of the HELLP patients and in 75 percent of the non-HELLP patients. When patients who were delivered within 48 hours are omitted from the calculation, the median prolongation of pregnancy was 15 (3-62) days in preeclamptic patients with HELLP compared with 17 (3-60) days in patients without HELLP; the difference is not statistically significant. Complete antepartum resolution of the HELLP syndrome, including normalization of liver enzymes, occurred in 55 of 106 patients not delivered within 48 hours. Blood pressure, proteinuria and laboratory data on admission of the 55 HELLP patients who had a complete antepartum reversal did not differ from those of the other HELLP patients. The 55 patients who showed complete antepartum reversal of HELLP had a median prolongation of pregnancy of 21 (7-62) days.

Maternal mortality did not occur. There were no maternal complications associated with the introduction or maintenance of the pulmonary artery catheter. In the majority of patients with HELLP, the upper abdominal pain disappeared within approximately three hours after the start of treatment. The bleeding problems of HELLP patients consisted of abdominal hematoma following cesarean section (n=10) and one postpartum uterine bleeding. At delivery 10 HELLP patients received platelet transfusion, in all other patients with HELLP who had a platelet count below $100x10^9/l$ at delivery, platelet counts returned to normal within two (1-10) days after delivery without platelet transfusions or any other treatment for the thrombocytopenia. Of the preeclamptic patients without HELLP one had hematemesis, five had a postoperative abdominal hematoma, and one had a hematoma of the vulva. In one of the patients with HELLP, eclampsia occurred during treatment; in the other cases eclampsia occurred shortly after admission, before the start of treatment.

Median birthweight and the number of low birthweight infants were not different between groups. Perinatal mortality, including all fetal deaths irrespective of birthweight, was similar in preeclamptic patients with HELLP (14 percent), and without HELLP (15 percent). There was no difference in perinatal mortality between patients (n=32) with platelet counts of less than $50x10^9/l$ (12.5 percent) and women (n=96) with platelet counts between $50\text{-}100x10^9/l$ (14.5 percent). All stillbirths, except one,

occurred in cases with severe fetal growth retardation at an early gestational age. Fetal distress was recognized in those cases, but no action was taken because the chance of neonatal survival was considered extremely small with a significant risk of severe neonatal morbidity. One preeclamptic patient with HELLP had a stillbirth with a birthweight of 2370 g at 34 weeks due to placental abruption.

Six of the eight neonatal deaths in the preeclamptic group without HELLP and six of the seven neonatal deaths in the HELLP group were caused by severe respiratory distress due to prematurity. Neonatal platelet counts were not different between groups. No significant correlations could be demonstrated between the last maternal platelet count before delivery and neonatal platelet count, either in patients with or in patients without HELLP. Cerebral hemorrhage was demonstrated in seven newborns, two born to preeclamptic patients with HELLP and five born to patients without HELLP. A baby with grade III cerebral hemorrhage on ultrasound was born at 29.4 weeks' gestation with a weight of 1120 g and a platelet count of $46x10^9/l$; of the other six infants with cerebral hemorrhage only one had a platelet count below $100x10^9/l$ at birth. Both babies with a cerebral bleed and platelets below $100x10^9/l$ were born to patients without HELLP.

7.4. Discussion

As yet it is not understood why some patients with preeclampsia or eclampsia develop the microangiopathic complications of hemolysis, platelet activation and consumption, and deposition of fibrin in liver sinusoids and areas of hepatocellular necrosis leading to the clinical triad of HELLP[141]. Also the cause of the extreme variability of the clinical expression of HELLP and of its association with pregnancy-induced hypertensive disorders is unknown. Some or all of the abnormal laboratory tests that characterize HELLP may be found in the absence of hypertension and proteinuria, which may or may not develop at a later stage[131,140,141]. The development of HELLP up to seven days post partum has been reported[141,204].

In addition to the variable clinical expression of the syndrome, marked differences in diagnostic criteria applied in various studies have contributed to the controversy surrounding the incidence and clinical course in patients with HELLP[200,204]. Although most reports[130,180,208,218,224,236] claim to follow Weinstein's[237] criterion of a

platelet count of $< 100x10^9/l$ as indicating thrombocytopenia, patients with platelets above 100 are also included in many of these studies. The choice of liver enzymes considered to be diagnostic, and the threshold for pathologic levels are not defined[130,180] or vary considerably among authors[218,224]. Hemolysis was not detected[34,90,218] or is not mentioned[130,180] in many of the published reports, and patients are said to have the ELLP syndrome[200]. It is also not apparent from most reports whether or not the abnormal laboratory tests of the HELLP syndrome coincided or occurred at different times in the same patient. These inconsistencies hamper the interpretation of published data with regard to the clinical course in patients with the HELLP/ELLP syndrome.

In our study we applied strict criteria of preeclampsia and HELLP. All patients studied had proteinuric preeclampsia on admission and, at the same time, thrombocytopenia, elevated concentrations of both ASAT and ALAT, and hemolysis as defined by evidence of red cell fragmentation in the peripheral blood smear. The presence of hemolysis was supported by the markedly reduced levels of haptoglobin and increased lactic dehydrogenase (LDH) levels. LDH was not used in the diagnosis of hemolysis, but only six of the HELLP patients (4.7 percent) had an LDH level below 320 U/l (2 SD above the mean in our hospital). The signs and symptoms of HELLP were also found as separate entities in preeclamptic patients without the complete HELLP triad. This indicates that the subset of patients selected for this study on the basis of a strict definition of HELLP constitutes an extreme of the broad spectrum of severity of microangiopathic disease in preeclampsia.

In 61 percent of preeclamptic patients with HELLP platelet counts rose to $> 100x10^9/l$, and 43 percent showed complete resolution of the hemolysis, elevation of liver enzymes, and thrombocytopenia, before delivery. Partial or complete reversal of the HELLP syndrome has been reported by other investigators[34,79,90,130,133,218] and the contribution in our patients of volume expansion and antihypertensive treatment to the resolution of HELLP remains speculative. However, it should be noted that delayed resolution of HELLP after delivery, a severe complication for which exchange plasmapheresis with fresh-frozen plasma has been recommended[137], was not observed in our patients.

The process of platelet and red cell destruction and consumption at the microvascular level may activate the coagulation cascade[141], but the occurrence of DIC

in preeclamptic patients, with or without HELLP, remains controversial mainly because of disparate criteria and definitions. The only abnormal coagulation test observed in 42 percent of our preeclamptic patients with HELLP on admission was an antithrombin III concentration of less than 80 percent. In combination with the reduced platelet count, these patients met the criterion of two abnormal tests for the diagnosis of suspected DIC, but the three abnormal tests, required for the diagnosis of definitive DIC, were only found in three HELLP patients and one non-HELLP patient. These findings are in agreement with those reported by others[48,236] and indicate continuous, mild thrombin activation that does not result in a clinically relevant disturbance of coagulation. The rise in protein excretion that occurred in the majority of the preeclamptic patients in both groups during hemodynamic treatment may be due to plasma volume expansion, which is known to magnify proteinuria in patients with the nephrotic syndrome[199].

Using logistic regression analysis Romero et al.[187] showed that in patients with a pregnancy-induced hypertensive disorder a low platelet count was the best indicator of maternal, fetal and neonatal complications, and that the majority of neonatal complications were due to prematurity. This is not an unexpected finding because the presence of thrombocytopenia was considered an indication for immediate delivery irrespective of gestational age. For that reason, the number of neonatal complications may be considerably reduced by temporizing management with prolongation of pregnancy, provided that such an approach would not expose the mother to unacceptable risks. Based on the results obtained in the large group of preeclamptic patients reported in Chapter 6 of this thesis, the maternal risks of the invasive hemodynamic monitoring applied in the first one to three days of treatment appear to be small in our hands, and no undesirable side effects of manipulation of the maternal circulation were observed. This may, at least in part, be attributed to the small number of skilled operators involved, and to the presence in the obstetric intensive care unit of experienced medical and nursing staff, 24 hours per day and seven days per week.

The results obtained in our group of HELLP patients compare favorably with those in the largest series reported so far of 275 patients delivered immediately after admission at a mean gestational age of 32 weeks[140], with a maternal mortality of 1 percent and a perinatal mortality of 31 percent. Hemodynamic treatment was associated with marked objective and subjective improvement in maternal condition. Severe

complications of HELLP[200,204,237], such as liver rupture and renal failure, did not occur in our patients, but the sample size is too small to assess reliably these rare but life-threatening complications.

In conclusion, we cannot reject the hypothesis that the clinical course and outcome of temporizing treatment in patients with severe preeclampsia does not depend on the presence or absence of HELLP. The results of our study do not support a general recommendation of prompt termination of pregnancy in patients with HELLP, regardless of gestational age. Although temporizing management of preeclamptic patients appears to be safe and may benefit the mother, the fetus, and the neonate, the value of invasive hemodynamic monitoring and treatment should be substantiated or denied in controlled trials.

Chapter 8

PERINATAL RESULTS OF HEMODYNAMIC AND CONSERVATIVE TEMPORIZING TREATMENT IN SEVERE PREECLAMPSIA*

8.1. Introduction

In Chapter 4 of this thesis evidence was presented that, in comparison with normotensive pregnancy, preeclampsia in untreated patients is characterized by a disturbance of the maternal circulation with a contracted plasma volume, low cardiac output, and high systemic vascular resistance. The clinical experiments reported in Chapter 5 and studies by other investigators[74,91,233] have shown that the abnormal maternal hemodynamic condition can be corrected with plasma volume expansion combined with pharmacologic vasodilatation. Guided by invasive central hemodynamic monitoring this approach has been used for temporizing management of preeclamptic women in the second or early third trimester, as described in Chapters 6 and 7. The aim of such hemodynamic treatment is to prolong gestation in order to enhance fetal maturity and to reduce neonatal morbidity and mortality caused by preterm birth. Assessment of the results obtained in more than 200 consecutive patients with severe preeclampsia remote from term (Chapter 6), with or without the HELLP syndrome (Chapter 7), has provided strong evidence that correction of the disturbed maternal circulation with plasma volume expansion and pharmacologic vasodilatation under central hemodynamic monitoring and with careful surveillance of maternal and fetal condition may indeed benefit the mother, the fetus and the neonate. However, these studies are observational and lack a control group of preeclamptic patients managed expectantly without attempts to correct their pathologic hemodynamic state.

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Attempts to execute in the University Hospital Rotterdam (AZR) a randomized controlled trial of hemodynamic and conservative temporizing treatment of patients with early severe preeclampsia met with considerable ethical and practical problems. For that reason we resorted to a retrospective study using matched controls managed in another University Hospital, the AMC, in the Netherlands during the same period of time, according to an expectant protocol without volume expansion and central hemodynamic monitoring.

8.2. Subjects and methods

Selection of patients

The study population consisted of nulliparous women with severe preeclampsia admitted to the antenatal wards of the AZR between January 1, 1985 and December 31, 1988. The control group was selected from nulliparous preeclamptic women, admitted to the AMC between January 1, 1984 and December 31, 1988. Severe preeclampsia was defined as the occurrence after 20 weeks' gestation of a diastolic blood pressure of 100 mm Hg or more on two occasions at least 4 hours apart and proteinuria of 0,5 g/L or more. All patients selected for the study met the following criteria: 1. singleton pregnancy with a live fetus; 2. gestational age between 20 and 34 completed weeks of amenorrhea; 3. not in labor; 4. no antihypertensive medication on admission; 5. no known preexisting hypertensive, cardiac or renal disease. Patients in both groups were matched retrospectively according to gestational age on admission accepting a maximal difference of one week. The matching was done in both centers in a blinded fashion on coded patients, without knowledge of the course or outcome of pregnancy.

Management protocols

In both centers patients were managed according to protocols that were not changed during the study period. The aim of treatment was to reduce maternal morbidity and to prolong gestation in an attempt to reduce neonatal complications of preterm birth. Fetal condition was monitored by means of cardiotocography and ultrasound. Decisions to deliver were made by the attending obstetricians on the basis of their interpretation of the cardiotocogram or of maternal condition. No corticosteroids

were used to enhance fetal lung maturation.

Hemodynamic temporizing treatment (study group)

Patients were admitted to the obstetric intensive care unit for central hemodynamic monitoring with the use of a radial artery and a Swan-Ganz catheter, as described in Chapter 2. Patients with a pulmonary capillary wedge pressure (PCWP) of less than 10 mm Hg and/or a cardiac index below 3.5 $l.min^{-1}.m^{-2}$ received an intravenous infusion of pasteurized plasma at a rate of approximately 250 ml/hr to reach and maintain PCWP values of 10-12 mm Hg, and a cardiac index between 3.5 and 4.6 $l.min^{-1}.m^{-2}$. If, after volume expansion, cardiac index was still less than 3.5 and diastolic arterial blood pressure was 100 mm Hg or more, patients received an intravenous infusion of dihydralazine at a rate of 1 mg/hr, followed by hourly increments of 1 mg, until the cardiac index had reached a value between 3.5 and 4.6 $l.min^{-1}.m^{-2}$, diastolic blood pressure was between 90 and 100 mm Hg, and a systemic vascular resistance index of 2000 $dyn.s.cm^5.m^2$ or less had been obtained. When cardiac index and systemic vascular resistance had reached normal values but diastolic blood pressure was still 100 mm Hg or more, antihypertensive treatment with alpha-methyldopa was added. After a stable normal hemodynamic condition had been reached and maintained for 24-48 hours, the Swan-Ganz catheter was removed and the patient was transferred to the obstetric ward where antihypertensive treatment was continued in the doses established under hemodynamic monitoring. All patients kept bed rest and maternal condition was continuously assessed by monitoring blood pressure, fluid balance and laboratory values. Anticonvulsive treatment with diazepam was used in exceptional cases in which eclampsia was thought to be imminent or convulsions occurred. Diet was unrestricted. If preterm labor occurred and delivery was still to be postponed, uterine contractility was inhibited using intravenous fenoterol.

Conservative temporizing treatment (control group)

Patients were treated with complete bed rest, no intravenous fluids and a diet containing less than 400 mg sodium per 24 hours. In addition, patients with symptoms such as headache, upper abdominal pain or visual disturbances received phenobarbital orally 30 mg t.i.d.. Antihypertensive medication was given when diastolic arterial blood

pressure reached and remained at a level of 115 mm Hg or more. Alpha-methyldopa was the drug of choice, intravenous dihydralazine was used when the desired reduction in blood pressure was not obtained. Intravenous magnesium sulfate was administered as anticonvulsive treatment; intravenous tocolysis was not used.

End points of study

General patient characteristics, laboratory data on admission and the last laboratory data obtained before delivery were analyzed. Primary end points of the study were the number of days of prolongation of pregnancy, predefined maternal antepartum and postpartum complications (mortality, HELLP-syndrome, eclampsia, abruptio placentae, indication and mode of delivery, postpartum hemorrhage, pulmonary edema), and specified measures of fetal and neonatal outcome (birthweight, perinatal mortality, arteficial ventilation, bronchopulmonary dysplasia, cerebral bleeding) and major handicaps in both groups.

Perinatal mortality included all stillbirths and neonatal deaths occurring within 28 days of birth in fetuses with a birthweight of 500 g or more. Infants were defined as small-for-gestational age (SGA) when birth weight was below the 10th percentile according to gestational age for infants born in the Netherlands[107]. All infants were followed until the age of 1½ years. Major handicaps were defined as cerebral palsy, mental retardation, and severe visual or hearing defects.

Data analysis

The study design was based on intention to treat; all patients who were enrolled in the study were analyzed, also when they were delivered before the actual start of temporizing treatment. Data are presented as median and range, unless stated otherwise. Wilcoxon's rank-sum and rank-sign tests, and chi-square tests were used for statistical analysis, as appropriate. A p-value of less than 0.05 (two-tailed) was taken as the level of significance.

8.3. Results

Clinical characteristics

During the study period 68 consecutive patients who met the inclusion criteria for the study were admitted to the AZR, and 60 to the AMC. From the study group 57 patients could be matched with 57 patients in the control group. The characteristics of patients in both groups are shown in Table 8.1.

Table 8.1. *Clinical characteristics on admission.*

	Study Group n=57	Control Group n=57
Age (yrs)	27 (18 - 39)	26 (19 - 36)
Gestational age (wks)	31.1 (26.0-35.0)	31.1 (24.9-35.0)
Systolic blood pressure (mm Hg)	160 (130 - 230)	160 (125 - 220)
Diastolic blood pressure (mm Hg)	110 (100 - 140)	110 (100 - 140)
Proteinuria (g/L)	1.9 (0.5- 35.7)	1.9 (0.5 -44.2)
HELLP (n)	15	11
Eclampsia (n)	1	2

Values are median (range), or number, as appropriate.

There were no significant differences between groups with regard to the severity of the hypertension and the amount of proteinuria. The HELLP syndrome was defined as the simultaneous occurrence of a platelet count below $100x10^9/l$ and serum aspartate (ASAT) and serum alanine aminotransferases (ALAT) levels of 50 U/l or more. There was no difference in the incidence of HELLP or eclampsia on admission between groups. Of the 11 patients of the study group that could not be matched, gestational age was 27.0 (26.6-32.7) weeks, compared with 25 (24.1-34.9) weeks in the three non-matched control patients.

Laboratory data

Laboratory data obtained on admission are presented in Table 8.2. and at delivery in Table 8.3. Although there were statistically significant differences between the study and control groups on admission with regard to serum concentrations of

creatinine, sodium and potassium, aspartate aminotransferase (ASAT), lactate dehydrogenase (LDH), protein and albumen, the differences were small. Hemoglobin concentrations tended to fall during hemodynamic treatment and showed a significant rise in the control group. Uric acid levels did not change, but serum creatinine concentrations showed a significant increase in both groups. The amount of proteinuria doubled in patients under hemodynamic treatment, resulting in a significant fall in serum protein concentration; these changes were not observed in the control group.

Table 8.2. *Laboratory data on admission.*

		Study Group (n=57)	Control Group (n=57)	P
Hemoglobin	(mmol/L)	7.9 (6.2 - 10.7)	8.1 (6.5 - 9.6)	NS
Platelets	($x10^9$/L)	173 (13 - 334)	142 (23 - 334)	NS
Creatinine	(μmol/L)	72 (47 - 107)	65 (50 - 120)	<0.05
Uric acid	(mmol/L)	0.40 (0.25- 0.88)	0.41 (0.20-0.84)	NS
Sodium	(mmol/L)	140 (134 - 143)	135 (122 - 139)	<0.01
Potassium	(mmol/L)	4.4 (3.6 - 5.7)	4.2 (3.0 - 5.8)	<0.05
Proteinuria	(g/L)	1.9 (0.5 - 35.7)	1.9 (0,5 -44.2)	NS
ASAT	(u/L)	27 (11 - 765)	19 (3 - 998)	<0.05
ALAT	(u/L)	18 (5 - 348)	22 (2 - 642)	NS
LDH	(u/L)	341 (179 - 2985)	170 (15 - 1665)	<0.01
Serum protein	(g/L)	57 (45 - 71)	60 (48 - 78)	<0.01
Serum albumin	(g/L)	31 (24 - 38)	34 (25 - 42)	<0.01
Antithrombin III	(%)	83 (11 - 110)	80 (57 - 120)	NS

Values are median (range).

Maternal outcome

Fifty-one patients in the study group, and nine in the control group received antihypertensive medication. In deviation from the protocol, four patients in the study group were treated with intravenous labetalol instead of dihydralazine, as part of a clinical pilot study.

Table 8.3. *Laboratory data at delivery.*

		Study Group (n=57)	Control Group (n=57)	P
Hemoglobin	(mmol/L)	6.7 (5.5 - 9.3)	8.6 (7.2 - 10.6)	<0.01
Platelets	($x10^9$/L)	119 (20 - 395)	196 (22 - 330)	<0.01
Creatinine	(μmol/L)	76 (54 - 131)	76 (54 - 137)	NS
Uric acid	(mmol/L)	0.40 (0.23-0.68)	0.44 (0.20- 0.84)	NS
Sodium	(mmol/L)	139 (129 - 143)	134 (121 - 138)	<0.01
Potassium	(mmol/L)	4.3 (3.3 - 6.1)	4.4 (3.4 - 5.4)	NS
Proteinuria	(g/L)	3.7 (0.2 -46.6)	2.3 (0.1 - 44.2)	<0.05
ASAT	(u/L)	29 (12 - 219)	14 (3 - 1400)	<0.01
ALAT	(u/L)	20 (8 - 192)	10 (1 - 600)	<0.01
LDH	(u/L)	362 (176 -1280)	153 (67 - 1370)	<0.01
Serum protein	(g/L)	52 (44 - 68)	59 (48 - 76)	<0.01
Serum albumin	(g/L)	30 (21 - 40)	33 (25 - 40)	<0.01
Antithrombin III	(%)	74 (20 - 105)	85 (39 - 180)	<0.01

Values are median (range).

Maternal outcome is shown in Table 8.4. With 10-11 days the median prolongation of pregnancy obtained in both groups was similar. There were no complications attributable to central hemodynamic monitoring in the study group. Six patients in the study group and three of the control group developed HELLP during treatment; in five patients from the study as well as in five patients from the control group the signs of HELLP disappeared completely before delivery. Nine of the 14 pregnant women with HELLP in the control group and eight of the 21 HELLP patients in the study group had a normal platelet count before delivery.

Two patients in the study group and three in the control group developed eclampsia after admission, before the actual start of treatment. In one of the patients in the study group the convulsions were complicated by transient cortical blindness. Reversible renal insufficiency developed in the control group after delivery in two patients, one of whom needed temporary dialysis. Three patients in the study group had signs of incipient pulmonary edema with cardiac failure during treatment with intravenous fenoterol for tocolysis; they improved rapidly with diuretic treatment after tocolysis had been stopped.

Table 8.4. *Maternal outcome.*

	Study Group n=57	Control group n=57
Prolongation of pregnancy (days)	10 (0-57)	11 (0-64)
Termination within 48 hrs	8 (14%)	11 (19%)
Prolongation in remaining patients (days)	12 (3-56)	16.5 (3-64)
Maternal mortality	0	0
Maternal morbidity		
HELLP-syndrome	6	3
Eclampsia	2	3
Placental abruption	1	1
Pulmonary edema	3	0
Postpartum cardiomyopathy	1	1
Postpartum renal insufficiency	0	2
Mode of delivery		
Abdominal	46	39
Vaginal	11	18
Indication for delivery		
Spontaneous labor	9	11
Maternal condition	5	1
Fetal distress	30	31
Maternal condition + fetal distress	5	5
Fetal death	2	7
Advanced gestational age	6	2

Values are median (range), or number (percentage), as appropriate.

The mode of delivery did not differ between groups and was by cesarean section in 70-80 percent of cases. The occurrence of fetal distress was the indication for delivery in 52 percent of cases in both groups.

Perinatal and postnatal outcome

Fetal and postnatal data are summarized in Table 8.5. Gestational age at delivery was almost 33 weeks in both groups. Birthweight tended to be higher in the study group, but the difference was not statistically significant. However, the relative number of SGA infants was significantly smaller in hemodynamically treated patients than in controls, in particular the number of very low birthweight (< 2.3 percentile) babies.

Perinatal mortality in the study group was half that in the control group, but the difference was not statistically significant. In the study group, one fetal and one neonatal death occurred in the four patients treated with labetalol. In the two patients in the study group and in six of the seven patients with fetal death in the control group, fetal distress was recognized but it was decided not to deliver because of low estimated birthweight, a low chance of survival or a high estimated risk of major handicap. In the control group an unexplained fetal death occurred at 35.4 weeks.

Table 8.5. *Perinatal and postnatal outcome.*

	Study Group n=57	Control group n=57
Gestational age at delivery (wks)	32.9 (27.7-38.6)	32.7 (27.7-40.9)
Birthweight (g)	1330 (780-2450)	1215 (605-2800)
Birthweight percentile		
< P 10	29 (51%)	43 (75%)*
< P 5	13 (23%)	33 (58%)*
< P 2.3	5 (9%)	19 (33%)*
Perinatal mortality	7.1%	14.3%
Fetal deaths	2	7
gestational age (wks)	27.7-29.3	30 (27.7-35.4)
birthweight (g)	830 - 860	715 (630 - 1700)
Neonatal deaths	2	1
gestational age (wks)	28.3 - 31.9	30
birthweight (g)	960 - 1215	675
Deaths > 1 month after birth	1	0
Neonatal complications		
Cerebral bleeding		
grade I-II	2	2
grade III	1	0
Artificial ventilation	27	8*
duration of ventilation (days)	3 (1-74)	1.5 (1-10)
Bronchopulmonary dysplasia	5	2
Patent ductus arteriosus	9	2**
Sepsis	5	0
Major handicaps	2	0

* P < 0.01, ** P < 0.05
Values are median (range), or number (percentage), as appropriate.

Cerebral bleeding classified as grade III on ultrasound scan occurred in a baby in the study group born at 28.2 weeks' gestation with a weight of 960 g after unsuccessful antihypertensive treatment with labetalol. The infant developed severe respiratory and circulatory problems and died 8 days after birth. An infant in the study group with cerebral bleeding grade II had a birthweight of 1125 g at 30.5 weeks' gestation, after prolongation of pregnancy for 5 days. At the age of 1½ years the infant had cerebral palsy and a developmental delay. The other infants with cerebral bleeding showed normal psychomotor development at the age of 1½ years. In the study group more infants were ventilated than in the control group and complications due to patent ductus arteriosus or bronchopulmonary dysplasia occurred more often.

At 1½ years follow-up, two infants in the study group and none in the control group had a major handicap. One of the babies with a major handicap has been described above. The other infant was delivered vaginally at a gestational age of 33 weeks with a weight of 2050 g, and developed a severe respiratory distress syndrome

with circulatory arrest two days after birth. He was resuscitated, but suffered severe cerebral damage. At the age of one year the infant had a spastic quadriplegia. One baby of the study group, who was born at a gestational age of 32.1 weeks and who had a birthweight of 1100 g, developed bronchopulmonary dysplasia. Seven months after birth this baby died because of respiratory failure due to a common cold.

Perinatal outcome in non-matched patients

In the 11 patients in the study group who could not be matched, there was one stillbirth and one neonatal death. In the three patients in the control group who could not be matched, there were two stillbirths.

8.4. Discussion

Comparison of our results of temporizing treatment of patients with early severe preeclampsia with those reported in the literature is difficult. In many publications the severity of the disease or the gestational age on admission are not exactly reported[3,16,53,73]; often the gestational age on admission is not comparable between studies; and in many reports patients are excluded for various reasons that cannot be compared[16,139,149,160,161,162,179,203,206,207]. Also, because recent advances in perinatal care have markedly reduced neonatal morbidity and mortality, perinatal results obtained in recent years cannot be compared with those reported in earlier studies. There is, however, good agreement that the reported perinatal results are closely associated with gestational age at delivery[72,73,139,160,161,162,203,206,207,209]. For that reason, temporizing management resulting in prolongation of pregnancy may improve neonatal outcome.

Studies[160,162,206,207] in which a comparison between expectant and nonexpectant management was performed show that neonatal outcome was indeed improved by expectant management. Expectant management usually consists of bedrest, magnesium sulfate and antihypertensive therapy. We performed temporizing treatment with plasma volume expansion and vasodilatation and assessed the maternal and perinatal outcome of this approach with that of the usual expectant management. One other report could be found of temporizing treatment with hemodynamic monitoring using a Swan-Ganz catheter[91]. In 10 preeclamptic patients with a mean gestational age of 29 weeks on admission pregnancy was prolonged 0-13 days, with two perinatal deaths.

Because the number of preeclamptic patients treated in the AMC was somewhat smaller than that in the AZR, we had to add one more year to the control group. Values of blood pressure, proteinuria and serum uric acid levels on admission are similar in both groups, which indicates comparable severity of preeclampsia. Antihypertensive medication was used in 16 percent of the patients of the control group and in 89 percent of the patients of the study group which, accepting a similar severity of preeclampsia and absence of maternal hypertensive complications in both groups, may indicate that antihypertensive treatment was overused in the study group. The marked rise in protein excretion that occurred in the study group may be due to plasma volume expansion, which is known to magnify proteinuria in patients with the nephrotic syndrome[199].

Neither the number of days that pregnancy was prolonged, maternal morbidity and mortality, nor perinatal mortality differed significantly between both groups. In both groups the presence of the HELLP syndrome was not considered an indication for immediate delivery. The observation that platelet counts and liver enzymes returned to normal values during treatment in 24 percent of patients in the study group and 36 percent in the control group supports anecdotal data reported in the literature[34,90,130]. The improved maternal circulation in patients receiving plasma volume expansion may be responsible for the finding that none of the patients in the study group, compared with two in the control group, developed renal insufficiency, a known complication of preeclampsia.[150,179]

Pulmonary edema is a frequently reported complication of beta-agonist therapy, in particular in combination with volume expansion and in conditions in which an increased pulmonary capillary permeability could exist[85]. The observation that incipient pulmonary edema without signs of cardiac failure occurred in three patients receiving both plasma volume expansion and tocolytic treatment supports the view that this combination in preeclamptic patients is potentially dangerous and should be avoided[85].

Although perinatal mortality did not differ significantly between the study and the control group, it tended to be less in the study group. It is of note that two of the neonatal deaths in the study group occurred in infants whose mothers were treated with intravenous labetalol, a potent alpha and beta - adrenergic inhibitor. The neonates had intractable hypotension and bradycardia most likely due to adrenergic blockade, which may be deleterious in compromised preterm infants of the preeclamptic mother[87,241].

The number of very low birthweight infants was significantly smaller in the study group than in the controls. The severity of the disease and the duration of prolongation of pregnancy did not differ between both groups, which suggests that plasma volume expansion and vasodilatation may enhance fetal growth by improving placental perfusion. Improved fetal blood flow during plasma expansion therapy has been reported[103,210]. On the other hand, because this is not a randomized study the fetuses in the study group may have been less growth retarded on admission than in the control group because of differences with regard to referral practices.

Neonatal morbidity caused by respiratory and circulatory complications was significantly higher in the study group than in controls. This may be due in part to survival of more fetuses at risk in the study group, but differences in neonatal care between both centers may also be important. In the AMC, where the control group was delivered, the neonatal intensive care unit is next to the delivery suite, whereas at the time of the study in the AZR the neonatal intensive care unit was located in a different building and a neonate at risk was usually intubated prophylactically before transfer.

Plasma volume expansion and vasodilatation under central hemodynamic monitoring constitute invasive treatment which requires intensive care facilities and a skilled medical and nursing staff. If these prerequisites are met, treatment-related complications are rare[232]. The results obtained in both groups suggest that expectant, temporizing treatment of patients with early severe preeclampsia is safe and may even improve maternal condition. The good perinatal results in the control group support the view that temporizing treatment of preeclamptic patients may also be accomplished without plasma volume expansion and vasodilatation under hemodynamic monitoring. However, the smaller number of perinatal deaths and of severely growth-retarded infants in the study group suggest that there may be a subgroup of preeclamptic women who might benefit from hemodynamic temporizing management. Controlled studies are needed to further define or refute the existence of such a subgroup.

Chapter 9

COMPARISON BETWEEN THE HEMODYNAMIC EFFECTS OF ORAL NIFEDIPINE AND INTRAVENOUS DIHYDRALAZINE IN PATIENTS WITH SEVERE PREECLAMPSIA*

9.1. Introduction

Nifedipine is a calcium antagonist with a vasodilator effect on coronary and peripheral vessels[47,212]. It is potent and rapidly acting, even when administered orally, and is therefore recommended for use in hypertensive emergencies in nonpregnant[17,66,68,192] as well as in pregnant[72,110,125,234] patients. In nonpregnant patients the fall in blood pressure after oral nifedipine administration is closely related to pre-treatment blood pressures and therefore predictable, and the occurrence of severe hypotension is rare[212].

The drugs used most often for rapid reduction of blood pressure in pregnant patients with severe preeclampsia are hydralazine or dihydralazine[43,111]. The onset of action of (di)hydralazine after intravenous administration is between 20 and 30 minutes, the degree of blood pressure reduction is variable and unpredictable, and severe hypotension and even hypovolemic shock may occur[111,233]. Because of their contracted circulating volume, preeclamptic women are sensitive to the hypotensive effects of dihydralazine and those adverse effects can be avoided by combining (di)hydralazine administration with plasma volume expansion[12,233]. However, plasma volume expansion requires central hemodynamic monitoring to prevent inadvertent circulatory overload[233]. If the results with nifedipine reported in nonpregnant hypertensive patients also hold for

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pregnant women with severe preeclampsia, nifedipine could be a useful alternative for the treatment of hypertensive emergencies in these patients.

There are several reports[18,20,212] on the hemodynamic effects of nifedipine in nonpregnant hypertensive patients, but to the best of our knowledge no data concerning the central hemodynamic effects of nifedipine in hypertensive pregnant patients are available. We therefore designed the present study to compare the effects of a single oral dose of nifedipine with those of intravenous dihydralazine on central hemodynamics in pregnant women with severe preeclampsia.

9.2. Subjects and methods

Selection of patients

Twenty patients with severe preeclampsia and a live fetus between 27 and 35 weeks gestation admitted to the High Risk Obstetric Unit of the University Hospital Rotterdam participated in the study. Severe preeclampsia was defined as the occurrence after 20 weeks' gestation of a diastolic blood pressure of 110 mm Hg (Korotkoff 4) or more, and proteinuria of 0.5 g/l or more in a 24 hour urine collection. Before entrance to the study the blood pressure was measured at least three times during one hour. None of the patients had a history of preexisting hypertension or renal disease. On admission fetal condition as judged from the nonstress ultrasound Doppler cardiotocogram (CTG) was good and immediate delivery was not considered necessary by the attending obstetrician. The study protocol as approved by the University and Hospital Ethics Committee was explained and we obtained informed consent from each patient.

Invasive hemodynamic measurements

In the Obstetric Intensive Care Unit a pulmonary artery (Swan-Ganz) catheter and a radial artery line were placed as described in detail in Chapter 2. Maternal heart rate was determined from the continuously recorded electrocardiogram. Baseline hemodynamic values (systolic, diastolic and mean arterial pressures, right atrial and pulmonary capillary wedge pressures, heart rate, cardiac output and calculated systemic vascular resistance) were determined after a stabilization period of at least one hour after catheterization, approximately 10 minutes before the start of treatment. All

measurements were carried out with the patient in supine position.

Study Protocol

Patients with a pulmonary capillary wedge pressure (PCWP) of less than 8 mm Hg were given an intravenous infusion of pasteurized plasma at a rate of 250 ml/hr for volume expansion until they reached a PCWP of 8-10 mm Hg.

We asked 10 patients to chew a 10 mg capsule of nifedipine after the stabilization period. After 2 min we inspected the capsule for completeness of emptying. The other 10 patients received our standard antihypertensive treatment of dihydralazine by intravenous infusion at a rate of 1-3 mg/hr, titrated to obtain an intra-arterial diastolic blood pressure of 90 mm Hg within approximately 4 hrs. We determined systemic and pulmonary pressures, and heart rate, continuously for six hours, and measured PCWP and cardiac output (CO) at 4, 10, 15, 30, 60 minutes and than every hour until 6 hours after the start of treatment. Fetal condition was monitored continuously by Doppler ultrasound cardiotocography. During the measurements no other antihypertensive medication was used.

The cardiac output values and the calculated vascular resistances were indexed by body surface area calculated from the Dubois body surface area chart with the use of the actual height and weight of the patient as described in Chapter 2.

Data analysis

We analyzed measured hemodynamic variables using Wilcoxon's rank sum test for comparison between groups, and the rank sign test for comparison within groups. We used the Spearman test to assess the significance of correlations. A p-value of less than 0.05 (two-tailed) was considered statistically significant.

9.3. Results

Clinical characteristics

There were no differences between the nifedipine and dihydralazine-treated groups in the characteristics of the women on admission (Table 9.1.).

Table 9.1. *Clinical characteristics of preeclamptic patients in both groups.*

	nifedipine (n=10)	dihydralazine (n=10)
Nulliparous	5	8
Gestational age (wks)	30 (27 - 32)	32 (27 - 35)
Diastolic blood pressure (mmHg)	120 (110 - 140)	118 (110 - 140)
Proteinuria (g/l)	4.2 (1.5 - 14)	1.8 (0.5 - 20)

Values are median (range), or numbers, as appropriate.

Hemodynamic measurements

The baseline hemodynamic variables determined 10 min before the start of treatment were not statistically different between the groups (Table 9.2).

Table 9.2. *Baseline hemodynamic values in both groups.*

	nifedipine (n=10)	dihydralazine (n=10)
Heart rate (beats.min^{-1})	70 (60 - 80)	68 (59 - 109)
Systolic intra-arterial pressure (mm Hg)	195 (165 - 232)	186 (164 - 195)
Diastolic intra-arterial pressure (mm Hg)	107 (97 - 125)	103 (97 - 119)
Pulmonary capillary wedge pressure (mm Hg)	12 (8 - 18)	12 (9 - 17)
Right atrial pressure (mm Hg)	6 (0 - 8)	5 (0 - 11)
Cardiac index (l.min^{-1}.m^{-2})	3.7 (3.2 - 4.7)	3.4 (1.9 - 4.4)
Stroke volume index (ml.beat^{-1}.m^{-2})	53 (47 - 68)	46 (29 - 64)
Systemic vascular resistance index (dyn.sec.cm^{-5}.m^{2})	3010 (2243 - 3520)	3337 (2287 - 5233)

Values are median (range).

Four women in the nifedipine group received plasma infusion (250-500 ml) to increase PCWP to 8-10 mm Hg, compared with none of the women treated with dihydralazine. No effect of plasma infusion on systemic arterial pressure could be discerned.

The hemodynamic changes obtained with nifedipine were similar in all 10

patients. Nifedipine caused a significant fall in systolic (-18 percent) and diastolic (-18 percent) arterial pressure. Arterial pressure started to fall 4 to 5 minutes after oral administration of nifedipine, reached a nadir in approximately 10 to 15 minutes, and then remained stable for 2 to 4 hours followed by a gradual rise (Fig 9.1.).

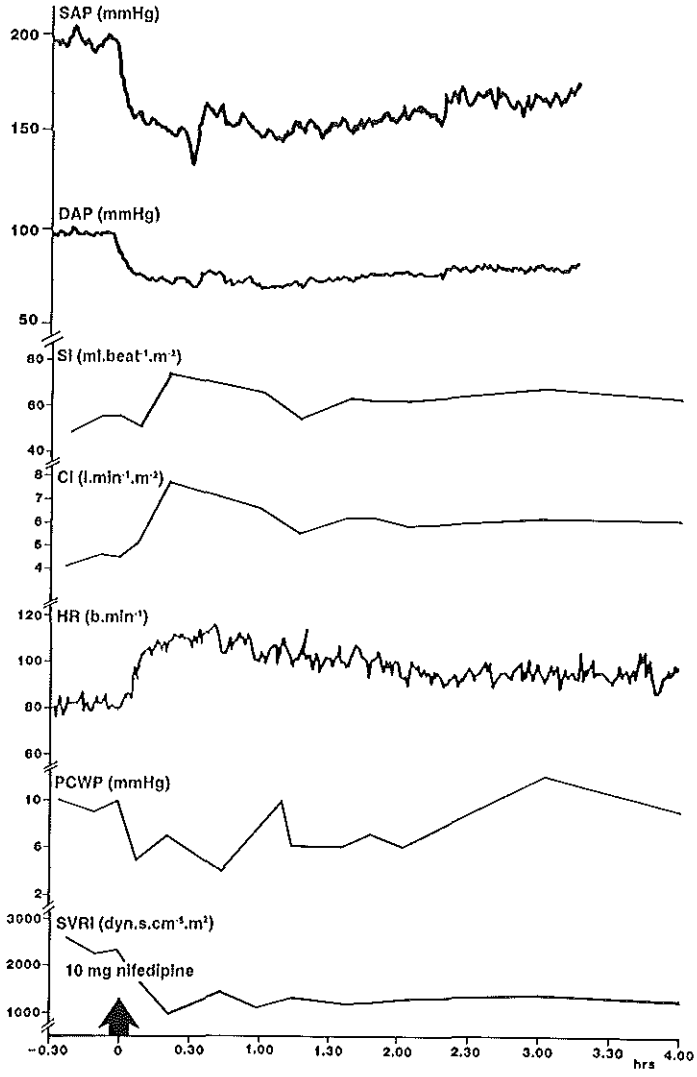

Fig 9.1. *An example of the hemodynamic effects of an oral dose of 10 mg of nifedipine in a preeclamptic patient. SAP = Systolic intra-arterial pressure; DAP = Diastolic intra-arterial pressure; SI = Stroke volume index; CI = Cardiac Index; HR = Heart rate; PCWP = Pulmonary capillary wedge pressure; SVRI = Systemic vascular resistance index*

Hypotension, defined as the occurrence of an intra-arterial diastolic blood pressure below 70 mm Hg, was not observed. We could not establish a relationship between the initial arterial pressure and the maximum drop in pressure. The maximum fall in blood pressure was associated with a significant increase in heart rate (+32 percent) and cardiac index (+46 percent), and with a significant reduction in systemic vascular resistance index (SVRI) (-44 percent) and PCWP (-30 percent).

Fig 9.2. shows a comparison between the maximum hemodynamic effects obtained in the 10 patients treated with nifedipine and those observed in the 10 other preeclamptic patients who received dihydralazine intravenously. The reduction in arterial blood pressure obtained with each agent was equal, and associated with a similar rise in heart rate and cardiac index, and a similar reduction in SVRI. The fall in PCWP after dihydralazine administration (-60 percent) was significantly greater than that obtained with nifedipine (-30 percent) ($p<0.02$). With nifedipine stroke volume index showed a tendency to increase (+13 percent) that did not reach statistical significance, whereas no effect of dihydralazine on stroke volume (-3 percent) was apparent.

In patients treated with nifedipine no signs of fetal distress were observed within the first 12 hours, whereas in the dihydralazine group the fetal CTG showed reduced variability and late decelerations in five cases. The subjective maternal side-effects of nifedipine were limited to mild headache in two patients. Of the women treated with dihydralazine, eight complained of severe headache, which was accompanied by nausea and vomiting in seven of them.

9.4. Discussion

To the best of our knowledge this is the first report on the effect of nifedipine on central hemodynamics in preeclamptic patients. Central hemodynamics in untreated preeclamptic patients are characterized by low to normal filling pressures, a low cardiac output and a high systemic vascular resistance (Chapter 4). These features were also observed in the patients in the present study, four of whom needed plasma volume expansion to increase their PCWP to the lower limit of normal. The hemodynamic effects of nifedipine in these preeclamptic patients consisted of a reduction in peripheral resistance associated with a simultaneous rise in cardiac output and heart rate. Also stroke volume tended to increase. The observation that severe hypotension did not occur

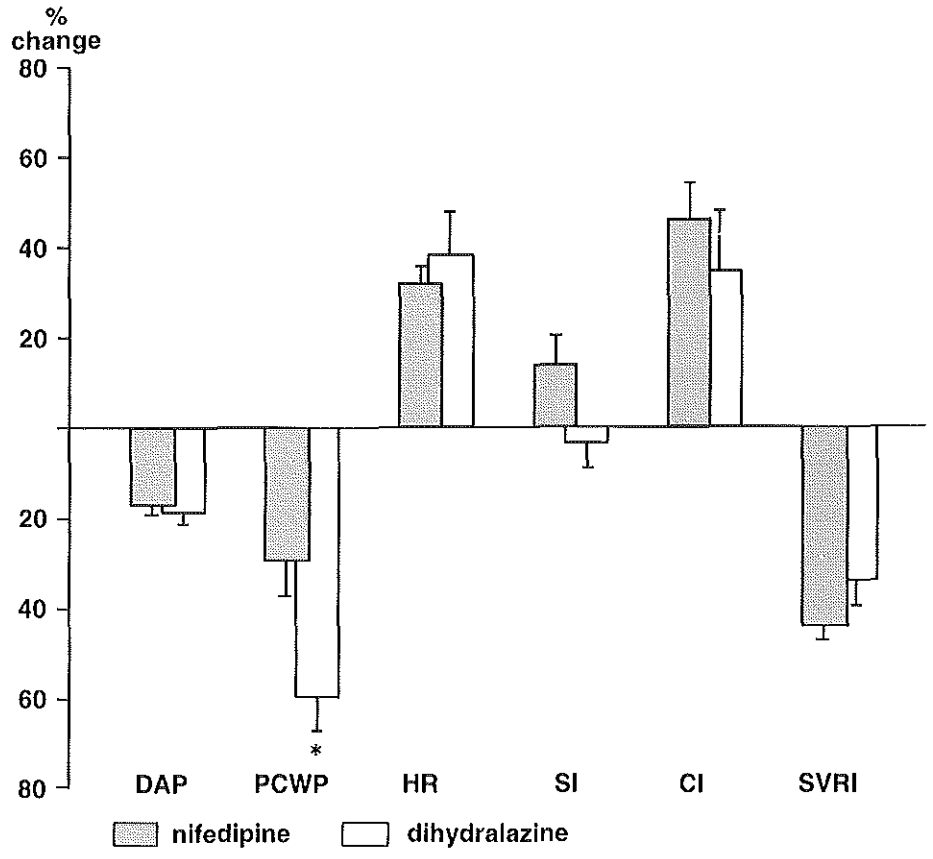

Fig 9.2. *Comparison between the mean (SEM) maximum change (%) in hemodynamic values in preeclamptic patients after an oral dose of 10 mg of nifedipine (n=10, solid bars) and after intravenous dihydralazine (n=10, open bars). DAP = Diastolic intra-arterial pressure; PCWP = Pulmonary capillary wedge pressure; HR = Heart rate; SI = Stroke volume index; CI = Cardiac index; SVRI = Systemic vascular resistance index *P<0.02*

is in accordance with most other studies[22,72,121,173,193,234], although there are two case reports of severe hypotension after oral nifedipine administration in preeclamptic patients[98,227]. In nonpregnant patients hypotension after nifedipine administration is rare and occurs mainly in hypovolemic patients[17,192]. The present study was performed in patients with normal filling pressures, and hypotension may occur more often in

severely volume-contracted preeclamptic women. Moreover, the two preeclamptic patients described by Waisman et al.[227], who became hypotensive after treatment with oral nifedipine were also treated with alpha-methyldopa and magnesium sulfate and the hypotension may have been caused by interaction of nifedipine with either drug. The time-related hypotensive response to nifedipine cannot be compared with that to dihydralazine, because the mode of administration of nifedipine was essentially different from that of dihydralazine.

The maximum effects of nifedipine and dihydralazine on systemic arterial blood pressure were similar, but PCWP decreased significantly less with nifedipine. Although both nifedipine[20] and dihydralazine[108] are dilators of the arterial vascular bed and have little action on the venous vasculature, the observation that PCWP decreased less with nifedipine suggests that the effect of nifedipine on the venous vascular bed could be even less than that of dihydralazine, which may be beneficial in the often volume-contracted preeclamptic patient. The rise in cardiac output with nifedipine administration was caused by a higher pulse rate and an increased stroke volume, although the latter did not reach statistical significance, whereas the rise in cardiac output after dihydralazine administration was caused exclusively by an increase in heart rate. The increase in stroke volume suggests an improvement of contractility with nifedipine.

It has been reported that nifedipine lowers blood pressure without reducing uteroplacental blood flow[121,136] and this might explain why the reduction in blood pressure with nifedipine in hypertensive pregnant patients is rarely associated with fetal distress[121,125,173,202,234]. Also in the present study no signs of fetal distress occurred in patients treated with nifedipine. In contrast, changes in the fetal CTG indicative of fetal distress were observed in half the number of patients treated with dihydralazine in accordance with the literature[72].

In conclusion, the hemodynamic effects of nifedipine could make it a useful antihypertensive agent for treatment of severe preeclampsia, in particular in hypertensive emergencies. Its advantages include effectiveness when administered orally, an almost immediate onset of hypotensive action, with a nadir after approximately 10-15 minutes and no further drop in pressure, potent selective vasodilatation, particularly pronounced in vessels with a high degree of vasoconstriction[17,212], and improvement of the maternal circulation without an apparent

deleterious effect on the uteroplacental circulation. However, it should be emphasized that the present study was carried out in patients with normal filling pressures, and uncompromised fetuses. Further investigations are needed to assess whether nifedipine is also safe in the volume-contracted preeclamptic patient, especially in those with severely growth-retarded fetuses.

CHAPTER 10

GENERAL CONCLUSIONS

In this chapter general conclusions will be presented, based on the studies reported in this thesis and related to the objectives outlined in Chapter 1. Various aspects of the study will be considered in the perspective of guidelines for the management of the patient with early onset severe preeclampsia, and recommendations for further research will be formulated.

10.1. Conclusions

1. In comparison with normotensive women in the early third trimester of pregnancy, central hemodynamics in untreated preeclamptic patients with a similar gestational age show a rather uniform pattern of low cardiac output, high systemic vascular resistance, and low to normal filling pressures. Baseline central hemodynamics in untreated preeclamptic women are more comparable with those in nonpregnant than in pregnant women. Reported extremes of the hemodynamic profile in preeclampsia, with high cardiac outputs and low systemic resistances, appear to be artefacts due to treatment.
2. Vasodilating agents used in the management of severe preeclampsia increase vascular space. Compensatory mechanisms may fall short resulting in insufficient perfusion of maternal organs, including the kidney and the uteroplacental unit. These adverse effects of hypotensive therapy may be avoided by correcting circulating volume by plasma volume expansion under central hemodynamic monitoring. By combining vasodilatation with dihydralazine and plasma volume expansion in preeclamptic patients, the disturbed hemodynamic state can be corrected, at least temporarily, and a hemodynamic profile can be obtained that is physiological for pregnancy.
3. Expectant management with plasma volume expansion and pharmacologic

vasodilatation under central hemodynamic monitoring of the maternal circulation may delay delivery and enhance fetal maturity, and it does not appear to be associated with an increased risk of maternal morbidity and mortality in patients with early onset preeclampsia without as well as with the syndrome of hemolysis, elevated liver enzymes, and a low platelet count (HELLP). The course and outcome of pregnancy in patients with severe preeclampsia receiving temporizing hemodynamic treatment does not depend on the presence or absence of HELLP. Temporizing treatment with plasma volume expansion and pharmacologic vasodilatation in patients with HELLP may improve fetal and neonatal as well as maternal outcome.

4. Temporizing treatment of preeclamptic patients may also be accomplished without plasma volume expansion and vasodilatation under central hemodynamic monitoring. However, there may be a subgroup of preeclamptic women who might benefit from hemodynamic temporizing treatment.

5. From the hemodynamic point of view nifedipine seems to be a useful agent in the treatment of hypertensive emergencies in pregnancy. Further studies are needed to assess if nifedipine is safe in the volume-contracted preeclamptic patient, especially in those with severely growth retarded fetuses.

10.2. Guidelines for management

Impressive hemodynamic changes take place in the course of maternal adaptation to pregnancy. A decrease in systemic vascular resistance accomodates a 40 percent increase in cardiac output, necessary to allow an increase in blood flow to various maternal organs, in particular the placenta and the kidneys. The studies presented in Chapter 4 provide evidence that the hemodynamic adaptation has become inadequate in the patient with established preeclampsia, who shows a return to the nonpregnant hemodynamic state. If maternal hemodynamic adaptation is considered essential for a normal course of pregnancy, symptomatic correction of the circulation of a preeclamptic patient may be expected to benefit the mother and the fetus. As shown in Chapter 5, plasma volume expansion combined with vasodilatation with dihydralazine, corrects the disturbed maternal circulation in preeclamptic patients in the early third trimester. After 2-3 days of hemodynamic stabilization in the obstetric intensive care unit, the vascular

catheters can be removed and the patient can be transferred to the antenatal ward, where antihypertensive treatment is continued in the doses established under hemodynamic monitoring.

We consider central hemodynamic monitoring an indispensible tool to assess the hemodynamic balance in patients with severe preeclampsia. Based on the results of the studies presented in this thesis the maternal risks of the invasive method of central hemodynamic monitoring applied in the first 1-3 days of treatment appear to be small in our hands. This may, at least in part, be attributed to the small number of skilled operators involved, and to the presence in the obstetric intensive care unit of an experienced medical and nursing staff, 24 hours per day and seven days per week.

As shown in the Chapters 6, 7 and 8, temporizing management based on correction of the maternal circulation with plasma volume expansion and pharmacologic vasodilatation under central hemodynamic monitoring may result in prolongation of pregnancy by 16 (range 0-62) days, and is associated with marked objective and subjective improvement in maternal condition. In pregnancies with a gestational age below 32 weeks a gain in duration of pregnancy of a single week may already improve perinatal outcome considerably (Table 6.5), which agrees with previous studies[162,184,207,239]. However, assessment of the perinatal results of prolongation of pregnancy in the observational studies reported in this thesis is hampered by the absence of an appropriate control group.

During the study period patients with preeclampsia in our center were not given corticosteroids to accelerate fetal lung maturation, because of lack of evidence of the presence of benefit and of the absence of adverse effects in these patients[42]. Because accumulated evidence now indicates that corticosteroids may indeed be beneficial[41,183], glucocorticoids are also used in preeclamptic patients since 1994 to accelerate fetal lung maturation. The use of corticosteroids may add to the beneficial effect of prolongation of pregnancy on neonatal outcome.

The earlier preeclampsia occurs, the more the fetus may benefit from prolongation of pregnancy, but despite hemodynamic temporizing treatment perinatal outcome in the patients with a gestational age below 26 weeks was poor. A possible explanation could be that the earlier the disease becomes clinically apparent, the more the fetoplacental unit has suffered, and irreversible placental damage may have

occurred.

For pharmacologic vasodilatation we chose (di)hydralazine, because this is the antihypertensive agent still recommended for the treatment of severe preeclampsia worldwide[10,43,111] and it has a firmly established safety record with regard to mother and fetus. Newer vasodilators, such as calcium channel blockers, may be useful in the management of preeclamptic patients, but their clinical application should await the results of appropriately controlled clinical trials on their efficacy and safety for the fetus, preferably with longterm follow-up of the newborns. Before such results are available, it seems safe to continue the use of (di)hydralazine as the drug of choice for antihypertensive treatment of preeclamptic patients.

10.3. Recommendations for further research

Controlled studies are necessary to assess the value of hemodynamic temporizing treatment in the management of patients with severe early-onset preeclampsia. Controlled trials of temporizing management, with and without the correction of the hemodynamic state under invasive central monitoring, can only be performed in centers with an obstetric intensive care unit, facilities for central hemodynamic monitoring, and experience in this kind of treatment. Unfortunately, as yet such centers are rare, although there is growing awareness of the need of obstetric intensive care units in the Netherlands as well as abroad[4,127,232]. Such studies should include assessment of the longterm developmental outcome in the children. Future studies on the effects of treatment on central hemodynamics should also evaluate the effects on the uteroplacental circulation. As yet studies about the effects of antihypertensive agents on the uteroplacental circulation[99,102] are scarce, mainly because of problems inherent in the assessment of uteroplacental flow[145,155,211,221]. In that respect, the use of color Doppler ultrasound looks promising[211,221].

Finally, future studies should address the important question if maintenance of maternal hypertension and proteinuria for an extended period of time could have an adverse effect on the recovery of the mother after delivery.

SUMMARY

CHAPTER ONE presents a general introduction to the thesis. Preeclampsia is a multi-organ dysfunction unique to human pregnancy. It is characterized by hypertension and proteinuria, and constitutes a major cause of maternal, fetal and neonatal mortality and morbidity worldwide. Preeclampsia represents a severe disturbance of the maternal circulatory adaptation to pregnancy, but published reports on hemodynamic profiles in preeclamptic patients are conflicting, and there is a lack of reference values obtained in normotensive pregnant women. Causal treatment consists of delivery of fetus and placenta, which may be associated with adverse neonatal effects due to prematurity. For that reason, symptomatic correction of the maternal circulation has been proposed in cases of early-onset preeclampsia in an attempt to postpone delivery. The effects of such hemodynamic temporizing treatment, consisting of pharmacologic vasodilatation and plasma volume expansion, on maternal central hemodynamics, and on the course and outcome of pregnancy are largely unknown. Based on the considerations presented in this chapter, the objectives of the studies reported in the following chapters are formulated and include an assessment of central hemodynamics in preeclamptic patients compared with those in normotensive pregnant women, an evaluation of the effects of symptomatic circulatory treatment on maternal central hemodynamics, and on course and outcome of pregnancy in patients with severe early preeclampsia, with and without the complication of the HELLP syndrome.

CHAPTER TWO deals with the methods of invasive monitoring of the systemic and pulmonary circulations, used to determine hemodynamic profiles in patients with severe preeclampsia and in normotensive controls, as reported in this thesis. Catheterization of the radial artery and insertion of the flow-directed balloon-tipped and temperature sensitive pulmonary artery (Swan-Ganz) catheter are described and the main advantages and potential complications of these invasive procedures are discussed.

CHAPTER THREE reports the results of invasive measurement of central hemodynamics in 10 healthy volunteers with an uncomplicated pregnancy of 28-30

weeks, with the aim to establish reference values for assessment of hemodynamic profiles in preeclamptic patients. Median (range) cardiac output was 7.4 (5.9-8.8)l.min^{-1} and cardiac output values showed a significant positive linear correlation with estimated body surface area. The left ventricular function curve revealed a hyperdynamic myocardial state in 70 percent of the women. No differences were demonstrated between hemodynamic values determined in supine and in left lateral position, but a simple hospital lunch appeared to cause a 14 percent rise in cardiac output.

CHAPTER FOUR describes a study in which central hemodynamic profiles in 87 preeclamptic patients between 25 and 34 weeks' gestation who had received no treatment at all were compared with those obtained in 47 preeclamptic women who were treated with various drugs and intravenous fluids. Median (range) cardiac index in the untreated patients of 3.3 (2.0-5.3) l.min^{-1}.m^{-2} was significantly lower than that in the treated patients of 4.3 (2.4-7.6), and than that in the normotensive pregnant women reported in Chapter 3 of 4.2 (3.5-4.6). Systemic vascular resistances in untreated preeclamptic patients were significantly higher than those in treated patients and in normotensive controls, but pulmonary capillary wedge pressures were not different between groups. Variability of all hemodynamic variables was much lower in untreated than in treated patients. The results indicate that untreated preeclamptic patients show a rather uniform pattern of a low cardiac index, a high systemic vascular resistance index, and normal filling pressures. The reported extremes of the hemodynamic profile in preeclampsia are artefacts due to treatment.

CHAPTER FIVE presents a study designed to determine the hemodynamic effects of dihydralazine infusion in preeclamptic patients with and without plasma volume expansion. Nineteen patients (group I) received dihydralazine first, followed by volume expansion, 19 patients (group II) received volume expansion followed by dihydralazine. In the first group dihydralazine caused a significant fall in mean arterial pressure, pulmonary capillary wedge pressure and systemic vascular resistance, with an increase in cardiac output, due to an increase in heart rate. Nine patients became oliguric and fetal distress occurred in seven cases. Following volume expansion pulmonary wedge pressure rose to normal values, cardiac output increased further and the systemic

vascular resistance fell. Urine production improved and fetal distress disappeared. In group II volume expansion had no effect on blood pressure, but was accompanied by a significant rise in pulmonary capillary wedge pressure and cardiac output. The rise in cardiac output was caused by a significant increase in stroke volume, without any change in heart rate. Urine production increased and no fetal distress was observed. The results show that the use of pharmacologic vasodilatation alone worsens the hypovolemic state in patients with preeclampsia, which may further compromise the placental circulation. These adverse effects of hypotensive therapy can be avoided by correcting circulating volume by plasma volume expansion.

CHAPTER SIX reports maternal and perinatal outcome in 254 consecutive patients with severe preeclampsia between 20 and 32 weeks' gestation, not in labor and with a live, single fetus, managed expectantly with vasodilatation by means of dihydralazine and plasma volume expansion under central hemodynamic monitoring. The median prolongation of pregnancy was 14 (range 0-62) days. Hemodynamic treatment was associated with marked objective and subjective improvement in maternal condition. Complications of central hemodynamic monitoring were not observed. Perinatal mortality was 20.5 percent. These data show that expectant management with plasma volume expansion and pharmacologic vasodilatation under central hemodynamic monitoring may delay delivery and enhance fetal maturity, and does not appear to be associated with an increased risk of maternal morbidity and mortality.

CHAPTER SEVEN describes a case controlled study to test the null hypothesis that the course and outcome of pregnancy in patients with severe preeclampsia receiving temporizing hemodynamic treatment does not depend on the presence or absence of the syndrome of hemolysis, elevated liver enzymes, and a low platelet count (HELLP). Hunderd and twenty-eight consecutive preeclamptic patients with HELLP with a duration of pregnancy of less than 34 weeks were matched for maternal and gestational age with 128 preeclamptic patients without HELLP. Both groups were treated with volume expansion and pharmacologic vasodilatation under invasive hemodynamic monitoring with the aim to prolong gestation and enhance fetal maturity. Except for variables pertaining to HELLP, clinical and laboratory data and median prolongation of

pregnancy did not differ between both groups. Complete reversal of HELLP occurred in 43 percent of patients. Perinatal mortality was 14.1 percent in HELLP patients and 14.8 percent in patients without HELLP. No maternal complications occurred. The data do not support a general recommendation of prompt termination of pregnancy in patients with HELLP, regardless of gestational age. Temporizing treatment may improve fetal and neonatal as well as maternal outcome in preeclamptic patients with HELLP.

CHAPTER EIGHT reports a study designed to compare maternal and perinatal outcome of hemodynamic and nonhemodynamic conservative management of severe preeclampsia. Fifty-seven preeclamptic women with a gestational age of 35 wks or less, treated with plasma volume expansion and vasodilatation under invasive hemodynamic monitoring, were matched with a control group of the same size of preeclamptic patients treated in another center without volume expansion and invasive monitoring. In both groups pregnancy was prolonged with 10-11 days. Maternal morbidity was low in both groups. No complications of hemodynamic monitoring were observed. Perinatal mortality was not significantly different between the study group (7.1 percent) and the control group (14.3 percent). Delivery of small-for-gestational age infants was significantly less frequent in the study group (9 percent) than in controls (33 percent). The results suggest that expectant, temporizing treatment of patients with early severe preeclampsia, with or without plasma volume expansion and invasive hemodynamic monitoring, may reduce neonatal mortality and morbidity. The difference in birthweight between study group and control group may be an effect of the therapy or may be caused by selection bias. The perinatal outcome in the study group suggests that there may be a subgroup of patients who might benefit from hemodynamic treatment.

CHAPTER NINE presents a prospective comparative study of the effects of a single oral dose of nifedipine and those of intravenous dihydralazine on central hemodynamics in women with severe preeclampsia. Ten patients chewed a 10 mg capsule of nifedipine, 10 patients received dihydralazine by intravenous infusion.

The reduction in arterial blood pressure obtained with both drugs was similar, and was associated with a similar rise in heart rate and cardiac output, and a similar reduction in systemic vascular resistance. Pulmonary capillary wedge pressures decreased

significantly less with nifedipine than with dihydralazine. Signs of fetal distress occurred in none of the nifedipine treated patients, but in five of the patients treated with dihydralazine. From the hemodynamic point of view nifedipine seems to be a useful agent in the treatment of hypertensive emergencies in pregnancy.

CHAPTER TEN presents general conclusions. In comparison with normotensive pregnant women, central hemodynamics in preeclamptic patients show a rather uniform pattern of a low cardiac output, high systemic vascular resistance and low to normal filling pressures. By combining vasodilatation with dihydralazine and plasma volume expansion in preeclamptic patients, the disturbed hemodynamic state can be corrected, at least temporarily, and a hemodynamic profile can be obtained that is physiological for pregnancy. With this approach it is possible to delay delivery and enhance fetal maturity, and it does not appear to be associated with an increased risk of maternal morbidity and mortality in patients with severe early onset preeclampsia. Future research with regard to temporizing hemodynamic treatment in severe early onset preeclampsia should be directed toward the assessment of longterm developmental outcome in the children and possible damage to the mother, preferably in controlled trials.

SAMENVATTING

HOOFDSTUK EEN geeft een algemene inleiding op het proefschrift. Preëclampsie is een aandoening waarbij een groot aantal orgaansystemen kunnen zijn betrokken. Het ziektebeeld is uniek voor de menselijke zwangerschap, wordt gekarakteriseerd door hypertensie en proteïnurie en is wereldwijd een belangrijke oorzaak van moederlijke, foetale en neonatale morbiditeit en mortaliteit. Bij preëclampsie is de aanpassing van de moederlijke circulatie aan de zwangerschap ernstig gestoord, maar gepubliceerde onderzoeken naar de hemodynamische verschijnselen bij preëclampsie spreken elkaar tegen en referentiewaarden van normotensieve zwangeren ontbreken. De causale behandeling bestaat uit het geboren laten worden van foetus en placenta, wat echter schadelijk kan zijn voor de pasgeborene wegens prematuriteit. Dit is de reden dat is voorgesteld om bij een vroeg in de zwangerschap optredende preëclampsie door middel van symptomatische correctie van de moederlijke circulatie de bevalling uit te stellen. De effecten van een dergelijke hemodynamische behandeling, bestaande uit farmacologische vasodilatatie en plasma volume expansie, op de moederlijke centrale hemodynamische waarden en op het beloop en de uitkomst van de zwangerschap zijn grotendeels onbekend. Op grond van de overwegingen beschreven in dit hoofdstuk worden doelstellingen geformuleerd van de onderzoeken die in de volgende hoofdstukken worden beschreven: het verkrijgen van centrale hemodynamische waarden van patienten met preëclampsie en vergelijking van deze waarden met die van normotensieve zwangeren; een evaluatie van de effecten van symptomatische behandeling op de moederlijke centrale hemodynamische waarden en op het beloop en de uitkomst van de zwangerschap bij patienten met een vroeg optredende ernstige pre-eclampsie, al dan niet gecompliceerd door het HELLP-syndroom.

HOOFDSTUK TWEE beschrijft de methoden voor invasieve bewaking van de systemische en pulmonale circulaties, die worden gebruikt voor het bepalen van de hemodynamische waarden bij patienten met ernstige preëclampsie en bij normotensieve controles. De catheterisatie van de arteria radialis en het inbrengen van de Swan-Ganz thermodilutie catheter worden beschreven en de belangrijkste voordelen en mogelijke

complicaties van deze invasieve procedures worden besproken.

HOOFDSTUK DRIE toont de centrale hemodynamische waarden, verkregen door middel van invasieve metingen bij 10 gezonde vrijwilligsters met een ongecompliceerde zwangerschap van 28-30 weken. Het doel van het onderzoek was het vaststellen van referentiewaarden voor evaluatie van het hemodynamische profiel van patienten met preëclampsie. Het hartminuutvolume was (mediaan) 7.4 (spreiding 5.9-8.8) $l.min^{-1}$ en toonde een significante, positieve, lineaire correlatie met het lichaamsoppervlak. De linkerventrikel functiecurve toonde een hyperdynamische myocardfunctie bij 70 percent van de vrouwen. Er werd geen verschil gevonden tussen de hemodynamische waarden gemeten in rugligging en op de linkerzij, maar een eenvoudige ziekenhuismaaltijd veroorzaakte een 14 percent stijging van de cardiac output.

HOOFDSTUK VIER beschrijft een onderzoek waarin de centrale hemodynamische waarden verkregen bij 87 onbehandelde zwangeren met preëclampsie en een zwangerschapsduur tussen de 25 en 34 weken worden vergeleken met die van 47 zwangeren met preëclampsie, die reeds waren behandeld met verschillende medicamenten en intraveneuze vloeistoffen. Het geindexeerde hartminuutvolume, mediaan 3.3 (spreiding 2.0-5.3) $l.min^{-1}.m^{-2}$ in de onbehandelde groep was significant lager dan dat van 4.3 (2.4-7.1) in de behandelde groep en dat van 4.2 (3.5-4.6) in de groep normotensieve zwangeren, besproken in Hoofdstuk 3. De systemische vaatweerstand was bij onbehandelde preëclamptische patienten significant hoger dan bij behandelde patienten en normotensieve controles, maar de pulmonale capillaire wiggedruk was niet verschillend. De variabiliteit van alle hemodynamische variabelen was veel lager bij onbehandelde dan bij behandelde patienten. De resultaten geven aan, dat onbehandelde preëclamptische patienten een vrijwel uniform patroon vertonen van een laag hartminuutvolume, een hoge systemische vaatweerstand en normale vullingsdrukken. De gerapporteerde extremen van hemodynamische waarden bij preëclampsie zijn artefacten veroorzaakt door behandeling.

HOOFDSTUK VIJF behandelt een onderzoek naar de hemodynamische effecten bij

preëclamptische patienten van dihydralazine infusie met en zonder plasma volume expansie. Negentien patienten (groep I) kregen eerst dihydralazine gevolgd door volume expansie, 19 patienten (groep II) kregen volume expansie gevolgd door dihydralazine. In de eerste groep veroorzaakte dihydralazine een significante daling van de gemiddelde bloeddruk, de pulmonale wiggedruk en de systemische vaatweerstand, met een toename van het hartminuutvolume tengevolge van stijging van de hartfrequentie. Negen patienten werden oligurisch en bij zeven trad foetale nood op. Na volume expansie werd de wiggedruk normaal, steeg het hartminuutvolume verder en daalde de weerstand. De urine produktie verbeterde en de foetale nood verdween. In groep II had volume expansie geen effect op de bloeddruk, maar veroorzaakte wel een significante stijging van wiggedruk en hartminuutvolume. De toename van het hartminuutvolume werd veroorzaakt door een significante stijging van het slagvolume, zonder verandering van de hartfrequentie. De urine produktie nam toe en er werd geen foetale nood geconstateerd. De resultaten tonen aan, dat farmacologische vasodilatie alléén de hypovolemische toestand bij patienten met preëclampsie verslechtert, wat een verdere vermindering van de de placentacirculatie kan bewerkstelligen. Deze bijwerkingen van antihypertensieve behandeling kunnen worden voorkomen door het circulerende volume te corrigeren met plasma volume expansie.

HOOFDSTUK ZES geeft een beschrijving van de maternale en perinatale resultaten verkregen bij 254 opeenvolgende patienten met ernstige preëclampsie en een zwangerschapsduur tussen 20 tot 32 weken, niet in partu en met een intacte éénling zwangerschap, die expectatief werden behandeld met vasodilatatie met behulp van dihydralazine en plasmavolume expansie onder centrale hemodynamische bewaking, met als doel het verlengen van de zwangerschap. De mediane verlenging van de zwangerschap was 14 (spreiding 0-62) dagen. De hemodynamische behandeling ging gepaard met een duidelijke objectieve en subjectieve verbetering van de moederlijke toestand. Complicaties van de centrale hemodynamische bewaking werden niet gezien. De perinatale mortaliteit bedroeg 20.5 percent. Deze resultaten tonen aan, dat een expectatieve behandeling met plasma volume expansie en farmacologische vasodilatatie onder centrale hemodynamische bewaking de bevalling kan uitstellen en de foetale rijping kan verbeteren en niet gepaard lijkt te gaan met een verhoogd risico op

moederlijke morbiditeit en sterfte.

HOOFDSTUK ZEVEN beschrijft een case-controle toetsing van de nulhypothese dat het beloop en de uitkomst van de zwangerschap bij patienten met ernstige preëclampsie en een temporiserende hemodynamische behandeling niet afhangt van de aan- of afwezigheid van het syndroom van hemolyse, verhoogde leverenzymen en een verlaagd aantal bloedplaatjes (HELLP). Honderdachtentwintig opeenvolgende preëclamptische patienten met HELLP en een zwangerschapsduur beneden de 34 weken werden gematched op maternale leeftijd en zwangerschapsduur met 128 preëclamptische patienten zonder HELLP. Beide groepen werden behandeld met volume expansie en farmacologische vasodilatatie onder invasieve hemodynamische bewaking, met als doel de zwangerschap te verlengen en de foetale rijping te bevorderen. Behalve de variabelen passend bij HELLP verschilden de klinische kenmerken, laboratorium uitslagen en de mediane verlenging van de zwangerschapsduur niet tussen de beide groepen. Volledig herstel van het HELLP syndroom trad op in 43 percent van de patienten. De perinatale sterfte bedroeg 14.1 percent bij de patienten met HELLP en 14.8 percent bij de patienten zonder HELLP. Er traden geen moederlijke complicaties op. Deze resultaten geven geen steun aan een algemene aanbeveling om de zwangerschap bij patienten met het HELLP syndroom snel te beëindigen, ongeacht de zwangerschapsduur. Temporiserende behandeling van patienten met HELLP kan zowel de foetale en neonatale alsook de maternale toestand verbeteren.

HOOFDSTUK ACHT beschrijft een onderzoek waarin de maternale en perinatale resultaten van hemodynamische en niet-hemodynamische temporiserende behandeling van ernstige preëclampsie worden vergeleken. Zevenenvijftig vrouwen met pre-ëclampsie en een zwangerschapsduur van 35 weken of minder, behandeld met plasma volume expansie en vasodilatatie onder invasieve hemodynamische controle, werden gematched met een even grote controlegroep van patienten met preëclampsie behandeld in een ander centrum zonder volume expansie en invasieve bewaking. In beide groepen werd de zwangerschap verlengd met 10-11 dagen. De moederlijke morbiditeit was in beide groepen laag, er werden geen complicaties van de hemodynamische bewaking gezien. Er was geen significant verschil in perinatale mortaliteit tussen de

onderzoeksgroep (7.1 percent) en de controlegroep (14.3 percent). In de onderzoeksgroep (9 percent) werden significant minder ernstig groei vertraagde kinderen geboren dan in de controlegroep (33 percent). De resultaten suggereren, dat expectatieve temporiserende behandeling van patienten met vroeg optredende ernstige preëclampsie met of zonder volume expansie en invasieve hemodynamische controle de neonatale mortaliteit en morbiditeit zou kunnen reduceren. Het verschil in geboortegewicht tussen de onderzoeks- en de controlegroep zou een gevolg van de behandeling, maar ook van selectie van patienten kunnen zijn. De perinatale resultaten in de studiegroep suggereren, dat er een sub-groep van patienten zou kunnen zijn, die in het bijzonder baat bij hemodynamische behandeling zou kunnen hebben.

HOOFDSTUK NEGEN geeft een beschrijving van een prospectief vergelijkend onderzoek naar de effecten van een éénmalige orale dosis nifedipine en van intraveneuze toediening van dihydralazine op de centrale hemodynamiek bij vrouwen met ernstige preëclampsie. Tien patienten kauwden een capsule van 10 mg nifedipine en 10 patienten ontvingen dihydralazine via intraveneuze infusie. De daling van de arteriële bloeddruk was bij beide medicamenten gelijk en ging gepaard met eenzelfde stijging van hartfrequentie en hartminuutvolume en een vergelijkbare afname van de systemische vasculaire weerstand. De pulmonale capillaire wiggedruk daalde significant meer met dihydralazine dan met nifedipine. Tekenen van foetale nood kwamen bij geen van de met nifedipine behandelde patienten voor, maar wel bij vijf patienten behandeld met dihydralazine. Uit hemodynamisch oogpunt lijkt nifedipine een nuttig middel te kunnen zijn voor behandeling van hypertensieve crisen in de zwangerschap.

HOOFDSTUK TIEN beschrijft de algemene conclusies. In vergelijking met normotensieve zwangeren hebben patienten met preëclampsie een laag hartminuutvolume, een hoge systeemweerstand en lage tot normale vullingsdrukken. Met vasodilatatie met behulp van dihydralazine in combinatie met plasmavolume expansie kan bij patienten met preëclampsie de gestoorde hemodynamische toestand worden gecorrigeerd tot voor de zwangerschap fysiologische waarden. Met dit beleid is het mogelijk de zwangerschap te verlengen en de foetus te doen rijpen, zonder dat het gepaard gaat met een verhoogde morbiditeit en mortaliteit van de moeder. Toekomstig

onderzoek op dit gebied moet worden gericht op de effecten van de hemodynamische temporiserende behandeling op de uteroplacentaire circulatie, op de ontwikkeling van het kind op langere termijn en op de eventuele schadelijke effecten die de moeder zou kunnen ondervinden op haar herstel na de bevalling. Deze doelstellingen dienen bij voorkeur te worden bereikt door middel van gecontroleerd klinisch onderzoek.

REFERENCES

1. Abdulla AM, Kavouras T, Rivas F, Stefadouros MA. Determination of mean pulmonary capillary pressure by a noninvasive technique. JAMA 1980; 243: 1539-1542.
2. Agee KR, Balk RA. Central venous catheterization in the critically ill patient. Crit Care Clin 1992; 8: 677-697.
3. Andersen WA, Harbert GM. Conservative management of pre-eclamptic and eclamptic patients: A re-evaluation. Am J Obstet Gynecol 1977; 129: 260-266.
4. Anthony J, Johanson R, Dommisse J. Critical care management of severe pre-eclampsia. Fetal Med Rev 1994; 6: 219-229.
5. Arnow PM, Costas CO. Delayed rupture of the radial artery caused by catheter-related sepsis. Rev Infect Dis 1988; 10: 1035-1037.
6. Askenazi J, Koeningsberg DI, Ziegler JH, Lesch M. Echocardiographic estimates of pulmonary artery wedge pressure. N Eng J Med 1981; 305: 1566-1568.
7. Bader RA, Bader ME, Rose DJ, Braunwald E. Hemodynamics at rest and during exercise in normal pregnancy as studied by cardiac catheterization. J Clin Invest 1955; 34: 1524-1536.
8. Band JD, Maki DG. Infections caused by arterial catheters used for hemodynamic monitoring. Am J Med 1979; 67: 735-741.
9. Barr PO. Percutaneous puncture of the radial artery with a multi-purpose Teflon catheter for indwelling use. Acta Physiol Scand 1961; 51: 343-347.
10. Barron WM. Hypertension. In: Barron WM, Lindheimer MD eds. Medical disorders during pregnancy. St Louis: Mosby year book, 1991: 1-41.
11. Belfort MA, Anthony J, Buccimazza A, Davey DA. Hemodynamic changes associated with intravenous infusion of the calcium antagonist verapamil in the treatment of severe gestational proteinuric hypertension. Obstet Gynecol 1990; 75: 970-974.

12. Belfort M, Uys P, Dommisse J, Davey DA. Haemodynamic changes in gestational proteinuric hypertension: the effects of rapid volume expansion and vasodilator therapy. Br J Obstet Gynaecol 1989; 96: 634-641.

13. Belfort MA, Anthony J, Kirshon B. Respiratory function in severe gestational proteinuric hypertension: the effects of rapid volume expansion and subsequent vasodilatation with verapamil. Br J Obstet Gynaecol 1991; 98: 964-972.

14. Benedetti TJ, Kates R, Williams V. Hemodynamic observations in severe preeclampsia complicated by pulmonary edema. Am J Obstet Gynecol 1985; 152: 330-334.

15. Benedetti TJ, Cotton DB, Read JC, Miller FC. Hemodynamic observations in severe pre-eclampsia with a flow-directed pulmonary artery catheter. Am J Obstet Gynecol 1980; 136: 465-470.

16. Benedetti TJ, Benedetti JK, Stenchever MA. Severe preeclampsia-maternal and fetal outcome. Clin Exp Hypertens B 1982; 1 (2-3): 401-416.

17. Bertel O, Conen D, Radü EW, Müller J, Lang C, Dubach UC. Nifedipine in hypertensive emergencies. Br Med J 1983; 286: 19-21.

18. Bonaduce D, Ferrara N, Petretta M, Romano E, Postiglione M, Rengo F, Condorelli M. Hemodynamic study of nifedipine administration in hypertensive patients. Am Heart J 1983; 105: 865-867.

19. Branthwaite MA, Bradley RD. Measurement of cardiac output by thermal dilution in man. J Appl Physiol 1968; 24: 434-438.

20. Braunwald E. Mechanism of action of calcium-channel-blocking agents. New Eng J Med 1982; 307: 1618-1627.

21. Carroll GC. Blood pressure monitoring. Crit Care Clin 1988; 4: 411-434.

22. Chenoy R, Johanson R, Dilip M, Malla DS. Nifedipine sublingually: an effective treatment of severe hypertension in pregnancy. J Obstet Gynaecol 1992; 12: 167-168.

23. Chesley LC, Lindheimer MD. Renal hemodynamics and intravascular volume in normal and hypertensive pregnancy. In: Rubin PC ed. Hypertension in Pregnancy. Handbook of hypertension. Volume 10. Amsterdam: Elsevier Science Publishers, 1988: 38-65.

24. Chesley LC. Disseminated intravascular coagulation. In: Chesley LC ed. Hypertensive disorders in pregnancy. New York: Appleton-Century-Crofts, 1978: 88-118.

25. Chesley LC. History and epidemiology of preeclampsia-eclampsia. Clin Obstet Gynecol 1984; 27: 801-820.

26. Chesley LC. A short history of eclampsia. Obstet Gynecol 1974; 43: 599-602.

27. Clark SL, Cotton DB. Clinical indications for pulmonary artery catheterization in the patient with severe preeclampsia. Am J Obstet Gynecol 1988; 158: 453-458.

28. Clark VL, Kruse JA. Arterial catheterization. Crit Care Clin 1992; 8: 687-697.

29. Clark SL, Cotton DB, Lee W, Bishop C, Hill T, Southwick J, Pivarnik J, Spillman T, DeVore GR, Phelan J, Hankins GDV, Benedetti TJ, Tolley D. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 1989; 161: 1439-1442.

30. Clark SL, Cotton DB, Pivarnik JM, Lee W, Hankins GDV, Benedetti TJ, Phelan JP. Position change and central hemodynamic profile during normal third-trimester pregnancy and post partum. Am J Obstet Gynecol 1991; 164: 883-887.

31. Clark SL, Cotton DB, Gonik B, Greenspoon J, Phelan JP. Central hemodynamic alterations in amniotic fluid embolism. Am J Obstet Gynecol 1988; 158: 1124-1126.

32. Clark SL, Phelan JP, Greenspoon J, Aldahl D, Horenstein J. Labor and delivery in the presence of mitral stenosis: Central hemodynamic observations. Am J Obstet Gynecol 1985; 152: 984-988.

33. Clark SL, Greenspoon JS, Aldahl D, Phelan JP. Severe preeclampsia with persistent oliguria: management of hemodynamic subsets. Am J Obstet Gynecol 1986; 154: 490-494.

34. Clark SL, Phelan JR, Allen SH, Golde SR. Antepartum reversal of hematologic abnormalities associated with the HELLP syndrome. A report of three cases. J Reprod Med 1986; 31: 70-72.

35. Conway J, Lund-Johansen P. Thermodilution method for measuring cardiac output. Eur Heart J 1990; 11 (suppl 1): S17-S20.

36. Cotton DB, Gonik B, Dorman K, Harrist R. Cardiovascular alterations in severe pregnancy-induced hypertension: Relationship of central venous pressure to pulmonary capillary wedge pressure. Am J Obstet Gynecol 1985; 151: 762-764.

37. Cotton DB, Gonik B, Dorman KF. Cardiovascular alterations in severe pregnancy-induced hypertension: Acute effects of intravenous magnesium sulfate. Am J Obstet Gynecol 1984; 148: 162-165.

38. Cotton DB, Longmire S, Jones MM, Dorman KF, Tessem J, Joyce TH. Cardiovascular alterations in severe pregnancy-induced hypertension: Effects of intravenous nitroglycerin coupled with blood volume expansion. Am J Obstet Gynecol 1986; 154: 1053-1059.

39. Cotton DB, Lee W, Huhta JC, Dorman KF. Hemodynamic profile of severe pregnancy-induced hypertension. Am J Obstet Gynecol 1988; 158: 523-529.

40. Cowley AJ, Stainer K, Murphy DT, Murphy J, Hampton JR. A non-invasive method for measuring cardiac output: the effect of Christmas lunch. Lancet 1986; 2: 1422-1424.

41. Crowley P. Corticosteroids prior to preterm delivery. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP eds. Pregnancy and childbirth module, 'Cochrane database of systematic reviews': Review No.02955. Oxford: Cochrane updates on disk, 26 April 1993.

42. Crowley P. Promoting pulmonary maturity. In: Chalmers I, Enkin M, Keirse MJNC eds. Effective care in pregnancy and childbirth. Volume 1. Oxford: Oxford University Press, 1989: 746-764.

43. Cunningham FG, Lindheimer MD. Hypertension in pregnancy. N Engl J Med 1992; 326: 927-932.

44. Dabestani A, Mahan G, Gardin JM, Takenaka K, Burn C, Allfie A, Henry WL. Evaluation of pulmonary artery pressure and resistance by pulsed Doppler echocardiography. Am J Cardiol 1987; 59: 662-668.

45. Daily EK, Tilkian AG. Hemodynamic monitoring. In: Tilkian AG, Daily EK eds. Cardiovascular procedures. Diagnostic techniques and therapeutic procedures. St Louis: The C.V. Mosby Company, 1986: 83-116.

46. Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. Am J Obstet Gynecol 1988; 158: 892-898.

47. Davidson RC, Bursten SL, Keeley PA, Kenny MA, Stewart DK. Oral nifedipine for the treatment of patients with severe hypertension. Am J Med 1985; 79 (suppl 4A): 26-30.

48. De Boer K, Büller HR, Ten Cate JW, Treffers PE. Coagulation studies in the syndrome of haemolysis, elevated liver enzymes and low platelets. Br J Obstet Gynaecol 1991; 98: 42-47.

49. De Swiet M, Talbert DG. The measurement of cardiac output by electrical impedance plethysmography in pregnancy. Are the assumptions valid? Br J Obstet Gynaecol 1986; 93: 721-726.

50. De Swiet M. The physiology of normal pregnancy. In: Rubin PC ed. Hypertension in pregnancy. Handbook of hypertension. Volume 10. Amsterdam: Elsevier Science Publishers, 1988: 1-9.

51. Dekker GA, Geijn HP van, Schuitemaker NWE, Dongen PWJ van, Bennebroek Gravenhorst J. Kan maternale sterfte tengevolge van preëclampsie/eclampsie worden voorkomen? Ned T Obstet Gynaecol 1993; 106: 273-277.

52. Department of Health. Report on confidential enquiries into maternal deaths in the United Kingdom 1985-1987. HMSO, London 1991.

53. Derham RJ, Hawkins DF, De Vries LS, Aber VR, Elder MG. Outcome of pregnancies complicated by severe hypertension and delivered before 34 weeks; stepwise logistic regression analysis of prognostic factors. Br J Obstet Gynaecol 1989; 96: 1173-1181.

54. Derham RJ, Robinson J. Severe preeclampsia: Is vasodilatation therapy with hydralazine dangerous for the preterm fetus? Am J Perinatol 1990; 7: 239-244.

55. Dildy GA, Cotton DB. Hemodynamic changes in pregnancy and pregnancy complicated by hypertension. Acute Care 1988-1989; 14-15: 26-46.

56. Dobb GJ, Donovan KD. Non-invasive methods of measuring cardiac output. Intensive Care Med 1987; 13: 304-309.

57. Donovan KD, Dobb GJ, Newman MA, Hockings BE, Ireland M. Comparison of pulsed Doppler and thermodilution methods for measuring cardiac output in critically ill patients. Crit Care Med 1987; 15: 853-857.

58. Douglas KA, Redman CW. Eclampsia in the United Kingdom. The 'BEST' way forward. Br J Obstet Gynaecol 1992; 99: 355-356.

59. Duvekot JJ, Peeters LLH. Maternal cardiovascular hemodynamic adaptation to pregnancy. Obstet Gynecol Surv 1994; 49: S1-S14.

60. Duvekot JJ, Cheriex EC, Pieters FAA, Menheere PPCA, Peeters LLH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. Am J Obstet Gynecol 1993; 169: 1382-1392.

61. Easterling TR, Watts H, Schmucker BC, Benedetti TJ. Measurement of cardiac output during pregnancy: validation of Doppler technique and clinical observation in preeclampsia. Obstet Gynecol 1987; 69: 845-850.

62. Easterling TR, Benedetti TJ. Preeclampsia: A hyperdynamic disease model. Am J Obstet Gynecol 1989; 160: 1447-1453.

63. Easterling TR, Schmucker BC, Benedetti TJ. The hemodynamic effects of orthostatic stress during pregnancy. Obstet Gynecol 1988; 75: 550-555.

64. Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: A longitudinal study. Obstet Gynecol 1990; 76: 1061-1069.

65. Editorial. Complications of pulmonary artery balloon flotation catheters. Lancet 1983; 1: 37-38.

66. Editorial. Hypertensive emergencies. Lancet 1991; 338: 220-221.

67. Ehlers KC, Mylrea KC, Waterson CK, Calkins JM. Cardiac output measurements. A review of current techniques and research. Ann Biomed Eng 1986; 14: 219-239.

68. Ellrodt AG, Ault MJ, Riedinger MS, Murata GH. Efficacy and safety of sublingual nifedipine in hypertensive emergencies. Am J Med 1985; 79 (suppl 4A): 19-25.

69. Fagard R, Staessen J, Amery A. The use of Doppler echocardiography to assess the acute haemodynamic response to felodipine and metoprolol in hypertensive patients. J Hypertens 1987; 5: 143-149.

70. Farinas PL. A new technique for the arteriographic examination of the abdominal aorta and its branches. Am J Roentgenol 1941; 46: 641-645.

71. Fegler G. Measurement of cardiac output in anaesthetized animals by a thermo-dilution method. Q J Exp Physiol 1954; 39: 153-164.

72. Fenakel K, Fenakel G, Appelman ZVI, Lurie S, Katz ZVI, Shoham ZEEV. Nifedipine in the treatment of severe preeclampsia. Obstet Gynecol 1991; 77: 331-337.

73. Ferrazzani S, Caruso A, De Carolis S, Martino IV, Mancuso S. Proteinuria and outcome of 444 pregnancies complicated by hypertension. Am J Obstet Gynecol 1990; 162: 366-371.

74. Gallery EDM, Delprado W, Györy AZ. Antihypertensive effect of plasma volume expansion in pregnancy-associated hypertension. Aust NZ J Med 1981; 11: 20-24.

75. Gallery EDM, Brown MA, Ross MR, Reiter L. Diastolic blood pressure in pregnancy: phase IV or phase V Korotkoff sounds? Hypertension in pregnancy 1994; 13: 285-292.

76. Gallery EDM, Hunyor SN, Györy AZ. Plasma volume contraction: a significant factor in both pregnancy-associated hypertension (preeclampsia) and chronic hypertension in pregnancy. Q J Med 1979; 48: 593-602.

77. Ganz W, Donoso R, Marcus HS, Forrester JS, Swan HJC. A new technique for measurement of cardiac output by thermodilution in man. Am J Cardiol 1971; 27: 392-396.

78. Gardner RM, Schwartz R, Wong HC, Burke JP. Percutaneous indwelling radial-artery catheters for monitoring cardiovascular function. Prospective study of the risk of thrombosis and infection. N Engl J Med 1974; 290: 1227-1231.

79. Goldberg I, Hod M, Katz I, Friedman S, Ovadia J. Severe pre-eclampsia and transient HELLP syndrome. J Obst Gynecol 1989; 9: 229-300.

80. Goodlin RC. HELLP does not always mean immediate HELP! Am J Obstet Gynecol 1990; 163: 1089.

81. Grasberger RC, Yeston NS. Less-invasive cardiac output monitoring by earpiece densitometry. Crit Care Med 1986; 14: 577-579.

82. Groenendijk R, Trimbos JBMJ, Wallenburg HCS. Hemodynamic measurements in preeclampsia: Preliminary observations. Am J Obstet Gynecol 1984; 150: 232-236.

83. Grunewald C, Nisell H, Carlström K, Kublickas M, Randmaa I, Nylund I. Acute volume expansion in normal pregnancy and preeclampsia: effects on plasma atrial natriuretic peptide (ANP) and cyclic guanosine monophosphate (cGMP) concentrations and feto-maternal circulation. Acta Obstet Gynecol Scand 1994; 73: 294-299.

84. Hankins GDV, Wendel GD Jr, Cunningham FG, Leveno KJ. Longitudinal evaluation of hemodynamic changes in eclampsia. Am J Obstet Gynecol 1984; 150: 506-512.

85. Hankins GDV. Complications of beta-sympathomimetic tocolytic agents. In: Clark SL, Phelan JP, Cotton DB eds. Critical care obstetrics. Oradell: Medical Economics Book, 1987: 192-207.

86. Hanneman LA. Hemodynamische bewaking. In: v.d.Brink G, Lindsen F, Rap H, Rijs B, Uffink Th eds. Intensive care verpleegkunde. Deel 1. Lochem: De Tijdstroom, 1991: 318-350.

87. Haraldsson A, Geven W. Severe adverse effects of maternal labetalol in a premature infant. Acta Paediatr Scand 1989; 78: 956-958.

88. Hays PM, Cruikshank DP, Dunn LJ. Plasma volume determination in normal and preeclamptic pregnancies. Am J Obstet Gynecol 1985; 151: 958-966.

89. Hellgren M, Egberg N, Eklund J. Blood coagulation and fibrinolytic factors and their inhibitors in critically ill patients. Intensive Care Med 1984; 10: 23-28.

90. Heyborne KD, Burke MS, Porreco RP. Prolongation of premature gestation in women with hemolysis, elevated liver enzymes and low platelets. A report of five cases. J Reprod Med 1990; 35: 53-57.

91. Hjertberg R, Belfrage P, Hägnevik K. Hemodynamic measurements with Swan-Ganz catheter in women with severe proteinuric gestational hypertension (pre-eclampsia). Acta Obstet Gynecol Scand 1991; 70: 193-198.

92. Hoar PF, Wilson RM, Mangano DT, Avery GJ, Szarnicki RJ, Hill JD. Heparin bonding reduces thrombogenicity of pulmonary-artery catheters. N Engl J Med 1981; 305: 993-995.

93. Hunter S, Robson SC. Adaptation of the maternal heart in pregnancy. Br Heart J 1992; 68: 540-543.

94. Hunyor SN, Flynn JM, Cochineas C. Comparison of performance of various sphygmomanometers with intra-arterial blood-pressure readings. Br Med J 1978; 2:159-162.

95. Hutton P, Dye J, Prijs-Roberts C. An assessment of the Dinamap 845. Anaesthesia 1984; 39: 261-267.

96. Hytten F. Blood volume changes in normal pregnancy. Clin Haematol 1985; 14: 601-612.

97. Ihlen H, Endresen K, Golf S. Cardiac stroke volume during exercise measured by Doppler echocardiography: comparison with the thermodilution technique and evaluation of reproducibility. Br Heart J 1987; 58: 455-459.

98. Impey L. Severe hypotension and fetal distress following sublingual administration of nifedipine to a patient with severe pregnancy induced hypertension at 33 weeks. Br J Obstet Gynecol 1993; 100: 959-961.

99. Janbu T, Nesheim B. The effect of dihydralazine on blood velocity in branches of the uterine artery in pregnancy induced hypertension. Acta Obstet Gynecol Scand 1989; 68: 395-400.

100. Johenning AR, Barron WM. Indirect blood pressure measurement in pregnancy: Korotkoff phase 4 versus phase 5. Am J Obstet Gynecol 1992; 167: 577-580.

101. Johnson CJH, Kerr JH. Automatic blood pressure monitors. A clinical evaluation of five models in adults. Anaesthesia 1985; 40: 471-478.

102. Jouppila P. Doppler findings in the fetal and uteroplacental circulation: A promising guide to clinical decisions. Ann Med 1990; 22: 109-113.

103. Karsdorp VHM, van Vught JMG, Dekker GA, van Geyn HP. Reappearance of end-diastolic velocities in the umbilical artery following maternal volume expansion: A preliminary study. Obstet Gynecol 1992; 80: 679-683.

104. Kerr MG, Scott DB, Samuel E. Studies of the inferior vena cava in late pregnancy. Br Med J 1964; 1: 532-533.

105. Kirkland LL, Veremakis C. Arterial pressure monitoring. In: Carlson RW, Geheb MA eds. Principles and practice of medical intensive care. Philadelphia: WB Saunders Company, 1993: 251-257.

106. Kitabatake A, Inoue M, Asao M, Masuyama T, Tanouchi J, Morita T, Mishima M, Uematsu M, Shimazu T, Hori M, Abe H. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. Circulation 1983; 68: 302-309.

107. Kloosterman GJ. On intrauterine growth. Int J Gynaecol Obstet 1970; 8: 895-912.

108. Koch-Weser J. Drug therapy-hydralazine. N Engl J Med 1976; 295: 320-323.

109. Kruse JA, Armendariz E. Hemodynamic monitoring. In: Carlson RW, Geheb MA eds. Principles and practice of medical intensive care. Philadelphia: WB Saunders Company, 1993: 1079-1103.

110. Kumar N, Batra YK, Bala I, Gopalan S. Nifedipine attenuates the hypertensive response to tracheal intubation in pregnancy-induced hypertension. Can J Anaesth 1993; 40: 329-333.

111. Kyle PM, Redman CWG. Comparative risk-benefit assessment of drugs used in the management of hypertension in pregnancy. Drug Safety 1992; 7: 223-234.

112. Ladner CN, Weston PV, Brinkman CR, Assali NS. Effects of hydralazine on uteroplacental and fetal circulations. Am J Obstet Gynecol 1970; 108: 375-381.

113. Lavine SJ, Held AC, Campbell CA, Johnson V. Utility of echophonocardiographic timing intervals for the prediction of left ventricular filling pressures. Am J Noninvas Cardiol 1989; 3: 249-254.

114. Lavine SJ. Noninvasive techniques. In: Carlson RW, Geheb MA eds. Principles and practice of medical intensive care. Philadelphia: WB Saunders Company, 1993: 1103-1120.

115. Lee W. Cardiorespiratory alterations during normal pregnancy. Crit Care Clin 1991; 7: 763-775.

116. Lee W, Rokey R, Cotton DB. Noninvasive maternal stroke volume and cardiac output determinations by pulsed Doppler echocardiography. Am J Obstet Gynecol 1988; 158: 505-510.

117. Lees MM, Scott DB, Kerr MG, Taylor SH. The circulatory effects of recumbent postural change in late pregnancy. Clin Sci 1967; 32: 453-465.

118. Levett JM, Replogle RL. Thermodilution cardiac output: a critical analysis and review of the literature. J Surg Res 1979; 27: 392-404.

119. Levy DM, Hinshaw K, Knox FM, Campbell DM, Sutherland HW. Cardiogenic pulmonary oedema: presentation of pre-eclampsia exacerbated by prostaglandin abortifacients. Br J Obstet Gynaecol 1994; 101: 263-265.

120. Lindheimer MD, Katz AI. Hypertension in pregnancy. New Eng J Med 1985; 313: 675-680.

121. Lindow SW, Davies N, Davey DA, Smith JA. The effect of sublingual nifedipine on uteroplacental blood flow in hypertensive pregnancy. Br J Obstet Gynaecol 1988; 95: 1276-1281.

122. Long PA, Abell DA, Beischer NA. Fetal growth retardation and pre-eclampsia. Br J Obstet Gynaecol 1980; 87: 13-18.

123. Lund CJ, Donovan JC. Blood volume during pregnancy. Significance of plasma and red cell volumes. Am J Obstet Gynecol 1967; 98: 393-403.

124. Lund-Johansen P, Omvik P. Hemodynamic patterns of untreated hypertensive disease. In: Laragh JH, Brenner BM eds. Hypertension: Pathophysiology, Diagnosis and Management. Volume 1. New York: Raven Press, 1990: 305-327.

125. Lurie S, Fenakel K, Friedman A. Effect of nifedipine on fetal heart rate in the treatment of severe pregnancy-induced hypertension. Am J Perinatol 1990; 7: 285-286.

126. Mabie WC, Ratts TE, Sibai BM. The central hemodynamics of severe preeclampsia. Am J Obstet Gyn 1989; 161: 1443-1448.

127. Mabie WC, Sibai BM. Treatment in an obstetric intensive care unit. Am J Obstet Gynecol 1990; 162: 1-4.

128. Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart Kl. A longitudinal study of cardiac output in normal human pregnancy. Am J Obstet Gynecol 1994; 170: 849-856.

129. MacGillivray I, Rose GA, Rowe B. Blood pressure survey in pregnancy. Clin Sci 1969; 37: 395-407.

130. MacKenna J, Dover NL, Brame RG. Preeclampsia associated with hemolysis, elevated liver enzymes, and low platelets - An obstetric emergency? Obstet Gynecol 1983; 62: 751-754.

131. Magann EF, Chauhan SP, Naef RW, Blake PG, Morrison JC, Martin JN Jr. Standard parameters of preeclampsia: Can the clinician depend upon them to reliably identify the patient with the HELLP syndrome? Aust NZ J Obstet Gynaecol 1993a; 33: 122-126.

132. Magann EF, Bass D, Chauhan SP, Sullivan DL, Martin RW, Martin JN Jr. Antepartum corticosteroids: Disease stabilization in patients with the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP). Am J Obstet Gynecol 1994; 171: 1148-1153.

133. Magann EF, Martin RW, Isaacs JD, Blake PG, Morrison JC, Martin JN Jr. Corticosteroids for the enhancement of fetal lung maturity: impact on the gravida with preeclampsia and the HELLP syndrome. Aust NZ J Obstet Gynaecol 1993b; 33: 127-130.

134. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. N Eng J Med 1977; 296: 1305-1309.

135. Mangano DT. Heparin bonding long-term protection against thrombogenesis. N Engl J Med 1982; 307: 894-895.

136. Mari G, Kirshon B, Moise KJ, Lee W, Cotton DB. Doppler assessment of the fetal and uteroplacental circulation during nifedipine therapy for preterm labor. Am J Obstet Gynecol 1989; 161: 1514-1518.

137. Martin JN Jr, Files JC, Blake PG, Norman PH, Martin RW, Hess LW, Morrison JC, Wiser WL. Plasma exchange for preeclampsia. I. Postpartum use for persistently severe preeclampsia-eclampsia with HELLP syndrome. Am J Obstet Gynecol 1990; 162: 126-137.

138. Martin JN Jr, Blake PG, Perry KG Jr, McCaul JF, Hess LW, Martin RW. The natural history of HELLP syndrome: Patterns of disease progression and regression. Am J Obstet Gynecol 1991; 164: 1500-1513.

139. Martin TR, Tupper WRC. The management of severe toxemia in patients at less than 36 weeks' gestation. Obstet Gynecol 1979; 54: 602-605.

140. Martin JN Jr, Perry KG Jr, Blake PG, Magann EF, Roberts WE, Martin RW. The presence of HELLP syndrome in the eclamptic parturient is a major maternal and perinatal risk indicator. Am J Obstet Gynecol 1993; 168: 386.

141. Martin JN Jr, Stedman CM. Imitators of preeclampsia and HELLP syndrome. Obstet Gynecol Clin North Am 1991; 18: 181-198.

142. Mashini IS, Albazzaz SJ, Fadel HE, Abdulla AM, Hadi HA, Harp R, Devoe LD. Serial noninvasive evaluation of cardiovascular hemodynamics during pregnancy. Am J Obstet Gynecol 1987; 156: 1208-1213.

143. Massa DJ, Lundy JS, Faulconer A, Ridley RW. A plastic needle. Mayo Clin Proc 1950; 25: 413-416.

144. Matsuda M, Sekiguchi T, Sugishita Y, Kuwako K, Iida K, Ito I. Reliability of non-invasive estimates of pulmonary hypertension by pulsed Doppler echocardiography. Br Heart J 1986; 56: 158-164.

145. Maulik DEV. Doppler ultrasound velocimetry for fetal surveillance. Clin Obstet Gynecol 1995; 38: 91-111.

146. McLennan FM, Haites NE, Rawles JM. Stroke and minute distance in pregnancy: a longitudinal study using Doppler ultrasound. Br J Obstet Gynaecol 1987; 94: 499-506.

147. Milsom I, Forssman L. Factors influencing aortocaval compression in late pregnancy. Am J Obstet Gynecol 1984; 148: 764-771.

148. Möller B, Lindmark G. Eclampsia in Sweden, 1976-1980. Acta Obstet Gynecol Scand 1986; 65: 307-314.

149. Moodley J, Koranteng SA, Rout C. Expectant management of early onset of severe pre-eclampsia in Durban. S Afr Med J 1993; 83: 584-587.

150. Moore MP, Redman CWG. Case-control study of severe pre-eclampsia of early onset. Br Med J 1983; 287: 580-583.

151. Mroczek WJ, Lee WR, Davidov ME. Effect of magnesium sulfate on cardiovascular hemodynamics. Angiology 1977; 28: 720-724.

152. Murray IP. Complications of invasive monitoring. Med Instrumentation 1981; 15: 85-89.

153. Nadeau S, Noble WH. Limitations of cardiac output measurements by thermodilution. Can Anaesth Soc J 1986; 33: 780-784.

154. National high blood pressure education program working group report on high blood pressure in pregnancy. Am J Obstet Gynecol 1990; 163: 1689-1712.

155. Neilson J, Grant A. Ultrasound in pregnancy. In: Chalmers I, Enkin M, Keirse MJNC eds. Effective care in pregnancy and childbirth. Volume I. Oxford University Press, Oxford; 1989: 419-439.

156. Nelson LD, Anderson HB. Patient selection for iced versus room temperature injectate for thermodilution cardiac output determinations. Crit Care Med 1985; 13: 182-184.

157. Newman B, Derrington C, Dore C. Cardiac output and the recumbent position in late pregnancy. Anaesthesia 1983; 38: 332-335.

158. Niclou R, Teague SM, Lee R. Clinical evaluation of a diameter sensing Doppler cardiac output meter. Crit Care Med 1990; 18: 428-432.

159. Norwood SH, Cormier B, McMahon NG, Moss A, Moore V. Prospective study of catheter-related infection during prolonged arterial catheterization. Crit Care Med 1988; 16: 836-839.

160. Odendaal HJ, Pattinson RC, Bam R, Grove D, Kotze TJ. Aggressive or expectant management for patients with severe preeclampsia between 28-34 weeks' gestation: a randomized controlled trial. Obstet Gynecol 1990; 76: 1070-1075.

161. Odendaal HJ, Pattinson RC, Du Toit R. Fetal and neonatal outcome in patients with severe pre-eclampsia before 34 weeks. S Afr Med J 1987; 71: 555-558.

162. Oláh KS, Redman CWG, Gee H. Management of severe, early pre-eclampsia: is conservative management justified? Eur J Obstet Gynecol Reprod Biol 1993; 51: 175-180.

163. Olsson B, Pool J, Vandermoten P, Varnauskas E, Wassen R. Validity and reproducibility of determination of cardiac output by thermodilution in man. Cardiology 1970; 55: 136-148.

164. Palmer AJ, Walker AHC. The maternal circulation in normal pregnancy. J Obstet Gynaecol Br Emp 1949; 56: 537-547.

165. Pattinson RC, Odendaal HJ, Du Toit R. Conservative management of severe proteinuric hypertension before 28 weeks' gestation. S Afr Med J 1988; 73: 516-518.

166. Perkins RP. Diazoxide in treatment of severe pre-eclampsia and hypertensive encephalopathy. Am J Obstet Gynecol 1976; 126: 296-297.

167. Perrino AC Jr, Barash PG. Concentric beam Doppler: Should we be going in circles? Crit Care Med 1990; 18: 456-457.

168. Petrie JC, O'Brien ET, Littler WA, de Swiet M. Recommendations on blood pressure measurement. Br Med J 1986; 293: 611-615.

169. Phelan JP. Obstetric critical care issues in prematurity. Clin Perinatol 1992; 19: 449-459.

170. Phelan JP, Yurth DA. Severe preeclampsia. I. Peripartum hemodynamic observations. Am J Obstet Gynecol 1982; 144: 17-22.

171. Phelan JP. Pulmonary edema in obstetrics. Obstet Gynecol Clin North Am 1991; 18: 319-331.

172. Pillay M, Moodley J. The HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome in severe hypertensive crises of pregnancy - does it exist? S Afr Med J 1985; 67: 246-248.

173. Pirhonen JP, Erkkola RU, Ekblad UU. Uterine and fetal flow velocity waveforms in hypertensive pregnancy: The effect of a single dose of nifedipine. Obstet Gynecol 1990; 76: 37-41.

174. Pomes Iparraguirre H, Giniger R, Garber VA, Quiroga E, Jorge MA. Comparison between measured and fick-derived values of hemodynamic and oxymetric variables in patients with acute myocardial infarction. Am J Med 1988; 85: 349-352.

175. Pritchard JA, Weisman R, Ratnoff OD, Vosburgh GJ. Intravascular hemolysis, thrombocytopenia and other hematologic abnormalities associated with severe toxemia of pregnancy. N Engl J Med 1954; 250: 89-98.

176. Rafferty TD, Berkowitz RL. Hemodynamics in patients with severe toxemia during labor and delivery. Am J Obstet Gynecol 1980; 138: 263-270.

177. Rafferty TD, Berkowitz RL. Complications of pulmonary artery catheterization in obstetric patients. Int J Gynaecol Obstet 1980; 18: 133-135.

178. Raftery EB. The methodology of blood pressure recording. Br J Clin Pharmacol 1978; 6: 193-201.

179. Railton A, Allen DG. Management and outcome of pregnancy complicated by severe pre-eclampsia of early onset. S Afr Med J 1987; 72: 608-610.

180. Rath W, Loos W, Kuhn W, Graeff H. The importance of early laboratory screening methods for maternal and fetal outcome in cases of HELLP syndrome. Eur J Obstet Gynecol Reprod Biol 1990; 36: 43-51.

181. Redman CWG. Pre-eclampsia and the placenta. Placenta 1991; 12: 301-308.

182. Riedinger MS, Shellock FG. Technical aspects of the thermodilution method for measuring cardiac output. Heart Lung 1984; 13: 215-222.

183. Roberts WE, Morrison JC. Pharmacologic induction of fetal lung maturity. Clin Obstet Gynecol 1991; 34: 319-327.

184. Robertson PA, Sniderman SH, Laros RK, Cowan R, Heilbron D, Goldenberg RL, Iams JD, Creasy RK. Neonatal morbidity according to gestational age and birth weight from five tertiary care centers in the United States, 1983 through 1986. Am J Obstet Gynecol 1992; 166: 1629-1645.

185. Robin ED. The cult of the Swan-Ganz catheter. Ann Intern Med 1985; 103: 445-449.

186. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial changes in pulmonary haemodynamics during human pregnancy: a non-invasive study using Doppler echocardiography. Clin Science 1991; 80: 113-117.

187. Romero R, Mazor M, Lockwood CJ, Emamian M, Belanger KP, Hobbins JC, Duffy T. Clinical significance, prevalence, and natural history of thrombocytopenia in pregnancy-induced hypertension. Am J Perinatol 1989; 6: 32-38.

188. Ross J, Braunwald E. The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin. Circulation 1964; 29: 739-749.

189. Rubler S, Damani PM, Pinto ER. Cardiac size and performance during pregnancy estimated with echocardiography. Am J Cardiol 1977; 40: 534-540.

190. Runciman WB, Ilsley AH, Roberts JG. An evaluation of thermodilution cardiac output using the Swan-Ganz catheter. Anaesth Intensive care 1981; 9: 208-220.

191. Schiff E, Friedman SA, Sibai BM. Conservative management of severe preeclampsia remote from term. Obstet Gynecol 1994; 84: 626-630.

192. Schillinger D. Nifedipine in hypertensive emergencies: a prospective study. J Emerg Med 1987; 5: 463-473.

193. Seabe SJ, Moodley J, Becker P. Nifedipine in acute hypertensive emergencies in pregnancy. S Afr Med J 1989; 76: 248-250.

194. Sehgal NN, Hitt JR. Plasma volume expansion in the treatment of pre-eclampsia. Am J Obstet Gynecol 1980; 138: 165-168.

195. Seneff M. Arterial line placement and care. In: Rippe JM, Irwin RS, Alpert JS, Fink MP eds. Intensive care medicine. Second edition. Boston: Little, Brown and Company, 1991: 37-47.

196. Seneff M. Central venous catheters. In: Rippe JM, Irwin RS, Alpert JS, Fink MP eds. Intensive care medicine. Second edition. Boston: Little, Brown and Company, 1991: 17-37.

197. Shah KB, Rao TLK, Laughlin S, El-Etr AA. A review of pulmonary artery catheterization in 6245 patients. Anesthesiology 1984; 61: 271-275.

198. Shellock FG, Riedinger MS. Reproducibility and accuracy of using room temperature vs. ice-temperature injectate for thermodilution cardiac output determination. Heart Lung 1983; 12: 175-176.

199. Shemesh O, Deen WM, Brenner BM, McNeely E, Myers BD. Effect of colloid volume expansion on glomerular barrier size-selectivity in humans. Kidney Int 1986; 29: 916-923.

200. Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): Much ado about nothing? Am J Obstet Gynecol 1990; 162: 311-316.

201. Sibai BM, Mabie BC, Harvey CJ, Gonzalez AR. Pulmonary edema in severe preeclampsia-eclampsia: Analysis of thirty-seven consecutive cases. Am J Obstet Gynecol 1987; 156: 1174-1179.

202. Sibai BM, Barton JR, Akl S, Sarinoglu C, Mercer BM. A randomized prospective comparison of nifedipine and bed rest versus bed rest alone in the management of preeclampsia remote from term. Am J Obstet Gynecol 1992; 167: 879-884.

203. Sibai BM, Spinnato JA, Watson DL, Hill GA, Anderson GD. Pregnancy outcome in 303 cases with severe preeclampsia. Obstet Gynecol 1984; 64: 319-325.

204. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer B, Friedman SA. Maternal morbidity and mortality in 442 pregnanies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J Obstet Gynecol 1993; 169: 1000-1006.

205. Sibai BM, Mabie WC. Hemodynamics of preeclampsia. Clin in Perinatol; 1991; 18: 727-747.

206. Sibai BM, Akl S, Fairlie F, Moretti M. A protocol for managing severe preeclampsia in the second trimester. Am J Obstet Gynecol 1990; 163: 733-738.

207. Sibai BM, Mercer BM, Schiff E, Friedman SA. Aggressive versus expectant management of severe preeclampsia at 28 to 32 weeks' gestation: A randomized controlled trial. Am J Obstet Gynecol 1994; 1: 818-822.

208. Sibai BM, Taslimi MM, El-Nazer A, Amon E, Mabie BC, Ryan GM. Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes and low platelets in severe preeclampsia-eclampsia. Am J Obstet Gynecol 1986; 155: 501-509.

209. Sibai BM, Taslimi M, Abdella TN, Brooks TF, Spinnato JA, Anderson GD. Maternal and perinatal outcome of conservative management of severe preeclampsia in midtrimester. Am J Obstet Gynecol 1985; 152: 32-37.

210. Siekmann U, Heilmann L, Klosa W, Quaas L, Schillinger H. Simultaneous investigations of maternal cardiac output and fetal blood flow during hypervolemic hemodilution in preeclampsia - preliminary observations. J Perinat Med 1986; 14: 59-69.

211. Soothill PW. Abnormalities of utero-placental and fetal Doppler studies. In: James DK, Steer PJ, Weiner CP, Gonik B eds. High risk pregnancy. Management options. London: WB Saunders Company, 1994: 771-781.

212. Sorkin EM, Clissold SP, Brogden RN. Nifedipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in ischaemic heart disease, hypertension and related cardiovascular disorders. Drugs 1985, 30: 182-274.

213. Spinnato JA, Sibai BM, Anderson GD. Fetal distress after hydralazine therapy for severe pregnancy-induced hypertension. Southern Med J 1986; 79: 559-562.

214. Stetz CW, Miller RG, Kelly GE, Raffin TA. Reliability of the thermodilution method in the determination of cardiac output in clinical practice. Am Rev Respir Dis 1982; 126: 1001-1004.

215. Strauss RG, Keefer JR, Burke T, Civetta JM. Hemodynamic monitoring of cardiogenic pulmonary edema complicating toxemia of pregnancy. Obstet Gynecol 1980; 55: 170-174.

216. Swan HJC, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. N Eng J Med 1970; 283: 447-451.

217. Swanson E, Freiberg A, Salter DR. Radial artery infections and aneurysms after catheterization. J Hand Surg 1990; 15: 166-171.

218. Thiagarajah S, Bourgeois FJ, Harbert GM, Caudle MR. Thrombocytopenia in preeclampsia: Associated abnormalities and management principles. Am J Obstet Gynecol 1984; 150: 1-7.

219. Thomas F, Burke JP, Parker J, Orme JF Jr, Gardner RM, Clemmer TP, Hill GA, MacFarlane P. The risk of infection related to radial vs. femoral sites for arterial catheterization. Crit Care Med 1983; 11: 807-812.

220. Thomasson B. Cardiac output in normal subjects under standard basal conditions. The repeatability of measurements by the Fick method. Scand J Clin Lab Invest 1957; 9: 365-376.

221. Trudinger BJ. Doppler ultrasonography and fetal well-being. In: Reece EA, Hobbins JC, Mahoney MJ, Petrie RH eds. Medicine of the fetus and mother. Philadelphia: JB Lippincott Company, 1992: 701-723.

222. Ueland K, Hansen JM. Maternal cardiovascular dynamics. II. Posture and uterine contractions. Am J Obstet Gynecol 1969; 103: 1-7.

223. Ueland K, Novy MJ, Peterson EN, Metcalfe J. Maternal cardiovascular dynamics. IV. The influence of gestational age on the maternal cardiovascular response to posture and exercise. Am J Obstet Gynecol 1969; 104: 856-864.

224. Van Dam PA, Renier M, Baekelandt M, Buytaert P, Uyttenbroeck F. Disseminated intravascular coagulation and the syndrome of hemolysis, elevated liver enzymes, and low platelets in severe preeclampsia. Obstet Gynecol 1989; 73: 97-102.

225. Vink GJ, Moodley J. The effect of low-dose dihydrallazine on the fetus in the emergency treatment of hypertension in pregnancy. S Afr Med J 1982; 62: 475-477.

226. Voyce SJ, Urbach D, Rippe JM. Pulmonary artery catheters. In: Rippe JM, Irwin RS, Alpert JS, Fink MP eds. Intensive care medicine. Second edition. Boston: Little, Brown and Company, 1991: 48-72.

227. Waisman GD, Mayorga LM, Cámera MI, Vignolo CA, Martinotti A. Magnesium plus nifedipine: potentiation of hypotensive effect in preeclampsia? Am J Obstet Gynecol 1988; 159: 308-309.

228. Wallenburg HCS, Visser W. Pregnancy-induced hypertensive disorders. Current Opin Obstet Gynecol 1994; 6: 19-29.

229. Wallenburg HCS. Detecting hypertensive disorders of pregnancy. In: Chalmers I, Enkin M, Keirse MJNC eds. Effective Care in Pregnancy and Childbirth. Volume 1. Oxford: Oxford University Press, 1989: 382-402.

230. Wallenburg HCS. Maternal haemodynamics in pregnancy. Fetal Med Rev 1990; 2: 45-66.

231. Wallenburg HCS, Kuijken JPJA. Effects of diazoxide on maternal and fetal circulations in normotensive and hypertensive pregnant sheep. J Perinat Med 1984; 12: 85-95.

232. Wallenburg HCS. Invasive hemodynamic monitoring in pregnancy. Eur J Obstet Gynecol Reprod Biol 1991; 42: S45-S51.

233. Wallenburg HCS. Hemodynamics in hypertensive pregnancy. In: Rubin PC ed. Hypertension in pregnancy. Handbook of Hypertension. Volume 10. Amsterdam: Elsevier Science Publishers, 1988: 66-101.

234. Walters BNJ, Redman CWG. Treatment of severe pregnancy-associated hypertension with the calcium antagonist nifedipine. Br J Obstet Gynaecol 1984; 91: 330-336.

235. Wasserstrum N, Kirshon B, Willis RS, Moise KJ Jr, Cotton DB. Quantitative hemodynamic effects of acute volume expansion in severe preeclampsia. Obstet Gynecol 1989; 73: 546-550.

236. Weinstein L. Preeclampsia/eclampsia with hemolysis, elevated liver enzymes, and thrombocytopenia. Obstet Gynecol 1985; 66: 657-660.

237. Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: A severe consequence of hypertension in pregnancy. Am J Obstet Gynecol 1982; 142: 159-167.

238. Weisel RD, Berger RL, Hechtman HB. Measurement of cardiac output by thermodilution. N Eng J Med 1975; 238: 682-684.

239. Wigton TR, Tamura RK, Wickstrom E, Atkins V, Deddish R, Socol ML. Neonatal morbidity after preterm delivery in the presence of documented lung maturity. Am J Obstet Gynecol 1993; 169: 951-955.

240. Wong DH, Mahutte CK. Two-beam pulsed Doppler cardiac output measurement: Reproducibility and agreement with thermodilution. Crit Care Med 1990; 18: 433-437.

241. Woods DL, Malan AF. Side effects of labetalol in newborn infants. Br J Obstet Gynaecol 1983; 90: 876.

242. Working group. National high blood pressure education program working group report on high blood pressure in pregnancy. Am J Obstet Gynecol 1990; 163: 1689-1712.

243. World Health Organization study group. The hypertensive disorders of pregnancy. WHO Tech Rep Ser 1987; 758: 1-114.

244. Yi JJ, Fullwood L, Stainer K, Cowley AJ, Hampton JR. Effects of food on the central and peripheral haemodynamic response to upright exercise in normal volunteers. Br Heart J 1990; 63: 22-25.

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