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Hypertensive disorders of pregnancy

P H P De Silva[a], **S Lanerolle**[b], **S H Dodampahala**[c], **R Silva**[d], **C Mathota**[e] ***on behalf of the Sri Lanka College of Obstetricians and Gynaecologists***

Correspondence: Sri Lanka College of Obstetricians and Gynaecologists, No. 112, Model Farm Road, Colombo 08.
E-mail: slcogoffice@gmail.com

Background

Hypertensive disorders of pregnancy (HDP) as a group, is one of the leading causes of both maternal and foetal perinatal mortality/morbidity and resultant long term-disability. It accounts for approximately 14% of all maternal deaths globally[1].

Hypertensive disorders of pregnancy broadly define a group of conditions closely associated with high blood pressure, proteinuria and/or seizures during pregnancy. Eclampsia is usually a consequence of pre-eclampsia consisting of central nervous system seizures which often leave the patient unconscious. If untreated, it can subsequently lead to death.

The serious consequences of such pre-eclampsia and eclampsia are associated with vasospasm, pathologic vascular lesions in multiple organ systems, increased platelet activation and subsequent activation of the coagulation cascade in the microvasculature[2].

In Sri Lanka, hypertensive disease has remained among the top five causes of maternal mortality for the last two decades[3]. While it has trended down in its significance as one of the top causes of maternal mortality, there is an inconsistent downward trend. Maternal hypertensive disease has reached the level of the top second cause of maternal mortality as recently as 2009 followed by a clearly observed down-trend until 2019, finally posting a fourth-highest cause of maternal mortality in Sri Lanka[3].

Preeclampsia complicates an approximate 2-8% of pregnancies world-wide. Even in resource-high countries, there has been an observed increase in the maternal deaths that can be attributed to hypertensive disorders[2].

Hypertensive disease is one of the causes that could be significantly modified to decrease its negative impact on maternal and neonatal health. This guideline is developed to aid in the dissemination of information with this objective in mind.

Pathophysiology

During an average pregnancy blood pressure generally falls by a detectable level in the first trimester and usually reaches a lowest level in the second trimester. It then rises back up to preconception pressure levels at term gestation.

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[a] *Consultant Obstetrician and Gynaecologist, Colombo North Teaching Hospital, Ragama, Sri Lanka*

[b] *Consultant Obstetrician and Gynaecologist, Castle Street Hospital for Women, Colombo 8, Sri Lanka*

[c] *Professor in Obstetrics and Gynaecology Department of Obstetrics and Gynaecology, University of Colombo, Sri Lanka*

[d] *Consultant Obstetrician and Gynaecologist, Colombo North Teaching Hospital, Ragama, Sri Lanka*

[e] *Consultant Obstetrician and Gynaecologist, Colombo North Teaching Hospital, Ragama, Sri Lanka*

Hypertensive disorders of pregnancy are classified by SLCOG as

1. Preeclampsia – Pregnancy specific disorder with Hypertension cured following the delivery of the conceptus.
2. Chronic hypertension – Hypertension pre-existing the pregnancy due to various causes.
3. Preeclampsia – Superimposed on chronic hypertension.
4. Hypertension discovered for the first-time during pregnancy without clinical criteria necessary for the diagnosis of preeclampsia – May or may not disappear after delivery.
5. Supra-physiological hypertension – Exaggerated physiological response in the latter part of the pregnancy in the presence of multiple pregnancies without other symptoms or signs of preeclampsia.

Hypertension is defined in pregnancy as systolic blood pressure greater than or equal to 140mmhg or a diastolic blood pressure of greater than or equal to 90mmHg or more, or both, on two occasions at least 4 hours apart after 20th weeks of gestation, in seated or left lateral position with at least ten minutes rest before the measurement was taken.

In a woman with a previously normal blood pressure, hypertension is considered to be severe when the systolic level reaches 160mmHg or the diastolic level reaches 110mmHg with a mean arterial pressure of more than 130mmHg even on one occasion.

Preeclampsia is defined as hypertension found for the first time during current pregnancy with significant proteinuria (300mg per 24 hours or urine Protein/ Creatinine ratio of 30 mg/mmol or more)[7]. If urine albumin to creatinine ratio is considered an alternative for the diagnosis of significant proteinuria, the cut-off value of 8mg /mmol is taken as the value for consideration[7].

It is not essential to have significant proteinuria for the diagnosis of preeclampsia (although it is the most commonly used supportive evidence for preeclampsia in the presence of significant hypertension). However, the absence of significant proteinuria, other parameters as given below with preeclampsia-specific organ involvement could use for the diagnosis of Preeclampsia. They are;

- Platelet count (Less than 100×10^9 /l)
- Liver profile (Elevation of liver transaminases twice the normal value)
- Renal insufficiency (creatinine more than 1.1 mg/dl or doubling of serum creatinine concentration observed in the absence of other renal disease)
- Exaggerated neurological reflexes
- Pulmonary oedema
- Foetal indicators: Such as growth retardation, reduction in liquor volume, CTG and doppler waveform-abnormalities are allowed to be used for the diagnosis of preeclampsia[7].

It is the clinical experience that after making the diagnosis of preeclampsia without proteinuria, most if not all patients subsequently develop proteinuria during the time taken for management of such pregnancies. Longer the time given, more developed the proteinuria.

In a case of preeclampsia, the aim is to control blood pressure values at about 140/90mmHg as further reduction has not shown to improve maternal or foetal outcome in preeclampsia.

As in any medical condition, identifying risk categories for development of preeclampsia and taking actions to prevent the onset or worsening of the disease is of great importance.

The major risk factors for preeclampsia are;

1. Preeclampsia in first pregnancy
2. Pre-existing renal disease
3. Autoimmune conditions such as APLS and SLE
4. Diabetes mellitus
5. Pre-existing hypertension

Any of the above factors are considered to be major indicators for the risk. Therefore, instituting antiplatelet therapy in the form of 75-150mg of aspirin is recommended[8].

Undermentioned factors are considered lesser risk factors for occurrence of preeclampsia.

In the presence of more than one such condition, it is advisable to start antiplatelet treatment in the form of 75-150 mg of aspirin from early second trimester until the birth of the baby.

1. First pregnancy age 35 years old
2. Pregnancy with an interval more than 10 years
3. BMI more than 35 kg/m^2 or more at first visit
4. Family history of preeclampsia
5. Multiple pregnancies

It is said that prophylactic aspirin therapy for above risk categories are preventive of preterm preeclampsia when aspirin is started between 12 and 20 weeks of gestation optimally before 16 weeks of gestation but it has not shown to reduce term-preeclampsia[6,7]. Although there is some evidence for early calcium supplementation in pregnancy with a favorable effect on preeclampsia, there are no accepted guidance for such by other recognized colleges and bodies[6,7].

It is recommended that achieving better control of pre-existing hypertension prior to planned pregnancy is beneficial. This has proven value in literature[7]. There are no recommendations for salt restriction to prevent preeclampsia or hypertension in pregnancy[6].

Control of blood pressure before pregnancy

It is recommended that any woman contemplating pregnancy, if possible, to have a preconception-health check, including the measurement of blood pressure. This is more important when the maternal age is advanced (more than 35 years), history of renal disease, relevant medical disorders or with family history of early onset hypertensive disorders. If hypertension is observed, taking steps to control it is recommended as well as looking for any underlying pathology.

If essential hypertension or anything else is diagnosed, management should be aimed at controlling the blood pressure to equal to less than 140/90, using anti-hypertensives considered safe in pregnancy. Any woman with the possibility of being pregnant planned or otherwise, should avoid ACE Inhibitors or AR Blockers.

If a woman gets pregnant while on ACE inhibitors or ARBs, take steps to stop such medications immediately and offer suitable alternatives. Hydrochlorothiazide is not recommended for this category of women as it has shown increased risk of congenital abnormalities and complications of the neonate when the drug is used in pregnancy.

As in any case of medically important high blood pressure management, weight management, exercise, modification of life-style leading to a stress-free life-style with sufficient rest, is advocated in hypertension in pregnancy.

When drug therapy is considered, the following drugs are proven for their efficacy and for their safety profile for the foetus. There are two categories of drugs. First used for long term control of blood pressure and the second group of drugs are used for rapidly lowering of blood pressure.

Elevations of both systolic and diastolic blood pressures are associated with negative maternal and foetal outcomes[1].

Control of blood pressure during Pregnancy

Once blood pressure elevation is diagnosed during pregnancy be it pre-existing hypertension or preeclampsia, the drugs used are not different. However, subcategories of safe medications, if taken by the patient prior to the pregnancy, need not change if that is safe in pregnancy (eg. metoprolol, verapamil, sotalol, carvedilol etc.)

Two types of medications are used for treatment of Hypertension in pregnancy:

1. Long-term control of blood pressure
2. Rapid lowering of blood pressure.

Drugs used for long term control of blood pressure

Taking the availability, cost and side effects of the drugs available in Sri Lanka, the drug of choice for control of blood pressure in pregnancy is oral nifedipine slow release tablets followed by methyldopa and labetalol[6].

Regarding pharmacotherapy for rapidly lowering of blood pressure in preeclampsia, use of hydralazine IV and labetalol IV or oral nifedipine is discussed in our previous guidance[10].

Labetalol IV is very scarce in Sri Lanka. However, it is to be considered the drug of choice in the absence of contraindications, for use in the presence of tachycardia as a manifestation of preeclampsia. IV hydralazine could make the condition of tachycardia worse.

Nifedipine used in rapidly controlling blood pressure is quick-release nifedipine which is not commonly available in Sri Lanka.

Cochrane review on all three drugs recently showed no difference between the efficacy[12,13].

Table 1. Outline of drugs commonly used in control of hypertension[14]

Drug – Mechanism of action	**Dose**	**Contraindications**	**Notes**
Methyldopa – Centrally acting	250-750 mg three times a day	Depression	Slow onset of action over 24 hours dry mouth sedation depression blurred vision Withdrawal: rebound hypertension
Labetolol – Beta blocker with mild alpha vasodilator effect	100-400 mg every 8 hours	Asthma Chronic airways limitation (COPD)	Bradycardia Bronchospasm Headache Nausea Scalp tingling (labetolol oly) which usually resolves within 24 hours
Nifedipine – Calcium channel antagonist	20-60 mg slow release twice a day	Aortic stenosis	Severe headache in first 24 hours Flushing Tachycardia Peripheral oedema Constipation
Hydralazine – Vasodilator	25-50 mg every 8 hours		Flushing Headache Nausea Lupus-like syndrome

Management of hypertension detected for the first time in pregnancy

Mild to moderate hypertension

It is advised to check blood pressure in seated or left lateral position with an appropriate blood pressure cuff, with an accurate mechanical or mercury sphygmomanometer, four hours apart for the confirmation of the diagnosis.

Once the diagnosis is confirmed of hypertension, basic preeclampsia screening should be carried on.

This includes

- Urine Full Report
- Urine Culture and Antibiotic Sensitivity Test
- Urine Protein Quantification
- Full Blood Count
- Blood Picture
- Serum Creatinine
- Liver Profile
- PT/INR is indicated only when other investigations are showing liver involvement

Uric acid is not usually tested. Though some suggest predictive value of uric acid level interpreted in relation to the gestation to correlate better with adverse events[14,15].

It is mandatory to check for foetal wellbeing with ultrasound scanning with emphasis on foetal biophysical profile, foetal doppler parameters and growth parameters. Further monitoring of foetus with a cardiotocographic tracing is essential. These would give an assessment of possible foetal effects of preeclampsia. In some cases foetal effects maybe the most significant finding other than the presence of hypertension.

Aim of management is to achieve maximum possible maturity of the foetus with no reasonable threat to the mother and the foetus. When the gestation is less than 34 weeks, the opinion is that it is unlikely to be favourable for achieving vaginal delivery though there are no contraindications for vaginal delivery because of the condition preeclampsia per se.

In the presence of hypertension, be it preeclampsia or not, delivery should be aimed at the completion of the 37th week of pregnancy. From the first time of detection of hypertension, until completion of 37 weeks of gestation, all patient's clinical characteristics need to be considered in deciding the time of delivery. This includes available infrastructure facilities of neonatal care, availability of the theater and available manpower resources.

In the absence of proteinuria and derangement of other above mentioned laboratory parameters identified as indicators of preeclampsia before the 35th week of pregnancy, prediction of onset of preeclampsia can be done using PlGF (Placental Growth Factor) alone or in comparison with soluble fms-like tyrosine kinase (sFlt-1). These blood tests are widely available for use in developed countries. Results from PELICAN study (Table 2) show a cut off value of 100 picogram/ml for PlGF as a high sensitivity test for women heading for preeclampsia which needs delivery within 14 days of the test.

The negative result would give confidence for outpatient management of women with hypertension with pregnancy. As these tests are not available in Sri Lanka, SLCOG Guidance Committee suggests outpatient management with no less than 14 days review appointments for women with hypertension in pregnancy in the absence of any other maternal, foetal, biochemical or ultrasound scan derangement of significance. The blood pressure control also need to be at a level for the satisfaction of the obstetrician concerned.

Though the 2019 NICE guideline gives an aim of keeping control of blood pressure 135/85 mmHg, there is controversy about the control need for mild to moderate hypertension in pregnancies even with preeclampsia. Treatment of blood pressure has not been shown to have prevented preeclampsia or perinatal outcomes. But the evidence shows reduction of development of severe blood pressure among treated women with mild blood pressure. Approximately 10 women need to be put on antihypertensive therapy to prevent one episode of severe hypertension[11].

However, uncontrolled spikes of blood pressure in untreated pregnancies may prompt action for delivery. Therefore, achieving blood pressure control by pharmaco-therapeutic means would facilitate prolongation of the pregnancy to achieve greater maturity of the foetus.

Table 2. PELICAN 2013 study results: Triage PlGF (Placental Growth Factor) test accuracy for predicting preeclampsia needing delivery within 14 days for women presenting between 20 weeks and 34 weeks plus 6 days gestation[7]

Test cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
<100pg/ml	0.96 (0.89 to 0.99)	.56 (0.46 - 0.63)	.44 (0.36 to 0.52)	.98 (0.93 to 1.00)
>/= 100pg/ml	0.96 (0.89 to 0.99)	.56 (0.49 to 0.63)	.43 (0.36 to 0.51)	.98 (0.93 to 1.00)
<fifth percentile	.96 (0.89 to 0.99)	0.56 (0.48 to 0.61)	0.43 (0.36 to 0.51)	.98 (0.93 to 1.00)
<12 pg/ml	0.63 (0.51 to 0.74)	0.90 (0.85 to 0.94)	0.70 (0.57 to 0.80)	0.87 (0.82 to 0.91)

Cochrane review of treatment has shown the possibility of clinically relevant reduction in preeclampsia related foetal or neonatal death particularly early pregnancy loss with treatment of mild to moderate hypertension in pregnancy. Antihypertensive therapy does not prevent preeclampsia (RR 0.99; 95% CI-0.84-1.18) or the associated adverse perinatal outcomes, but it decreases by half the incidence of development of severe hypertension among women with mild hypertension (RR 0.52; 95% CI-0.41 - 0.64)[11].

The focus of control, if antihypertensives are started, is aimed at achieving blood pressure targets between140-160 /90-100 mmHg, taking local practice and existence of hypertension predating pregnancy into consideration[11]. SLCOG recommends aiming to keep blood pressure at or below 150/100 mmHg.

Monitoring

In the absence of any investigative derangement of biochemical or foetal parameters, deviations of only the blood pressure which is judged to be controlled by the obstetrician. Repetition of full assessment of the patient inclusive of biochemistry and foetus is recommended in intervals not less than 14 days apart until the time of delivery.

In the presence of biochemical markers for systemic involvement, the patient is recommended for **in-ward patient care**. When a patient is admitted to a ward for preeclampsia, an obstetrician needs to review the patient **at least 72 hours apart**. Repetition of frequency of biochemistry depends on the available clinical data on the patient. Progression of the disease as indicated by investigative deterioration is to be considered important for more action: eg: Observed drop in platelet count even though the total count is over 100, mm^9/L or rising liver enzymes.

However, once significant proteinuria is observed, increasing the amount of protein is not indicative of outcome of preeclampsia.

When the delivery decision is taken, the appropriate mode of delivery would be decided by;

- The clinical picture
- Period of gestation
- Platelet count
- Liver involvement.

Patients with significant liver involvement or a drop in platelet count less than $70 \times 10^9/L^6$, should be delivered preferably in the presence of the specialist team.

NICE guidance does not recommend planned early birth before 37th week to a woman with chronic hypertension whose blood pressure is less than 160/110 mmHg with or without antihypertensive treatment unless there are other medical indicators.

If planned birth before completion of 37th is necessary a course of corticosteroids and magnesium sulfate is to be used if indicated.

Severe hypertension

Severe Hypertension is considered to be present when the blood pressure recorded is more than 160/110 mmHg or a Mean Arterial Pressure of more than 130 mmHg is detected in pregnancy. This could be due to any one of the above mentioned (1) - (4) hypertensive disorders of pregnancy. Eclampsia (or occurrence of seizures) is a common complication of severe hypertension though the relationship is not linear.

If eclampsia is present the SLCOG in keeping up with all available international guidance, recommends delivery as early as possible before 24 hours of occurrence of the first fit. For an ongoing convulsion, use of anticonvulsant agents such as IV magnesium sulfate is recommended.

Any woman who is being treated for severe hypertension whose birth is planned within the next 24 hours, consideration should be given for medication of intravenous magnesium sulfate. Following symptoms are recommended as points to consider magnesium sulfate treatment

- Severe headache
- Visual disturbance
- Nausea and vomiting
- Epigastric pain
- Oliguria
- Deterioration of laboratory parameters

(NICE 2010, amended 2019)

SLCOG recommends the use of collaborative eclampsia trial for administration of magnesium sulfate[7].

- A loading dose of 4g should be given intravenously over 5 to 15 minutes, followed by an infusion of 1g/hour maintained for 24 hours. If the woman has had an eclamptic fit, the infusion should be continued for 24 hours after the last fit.
- Recurrent fits should be treated with a further dose of 2-4 g given intravenously over 5 to 15 minutes [NICE 2010, amended 2019].
- Do not use diazepam, phenytoin or other anti-convulsants as an alternative to magnesium sulfate in women with eclampsia [2010, amended 2019].

Antihypertensive treatment is aimed at rapidly lowering blood pressure to a safer level. SLCOG recommends bringing down blood pressure to 150/100 or less with the use of medication recommended for rapidly lowering blood pressure. They are IV hydralazine, IV labetalol, oral nifedipine quick-release. Medication regimen is indicated in our previous guidance[10].

It is recommended to use a crystalloid load of 500ml prior to or concomitantly when drugs are used for rapidly lowering of blood pressure. This is very important especially in managing patients with oliguria but is not confined to the management of oliguria.

In women managed for preeclampsia with severe hypertension, decision of delivery should be considered when the foetal maturity is 35 weeks or more. But before 34 weeks +6 days if blood pressure control is achieved and laboratory parameters are favorable with due consideration of infrastructure and manpower and continuing pregnancy until 35 weeks is recommended with close scrutiny of the patient every 24 hours.

Mode of delivery when decided should be done on the clinical criteria, available infrastructure and monitoring facilities in consultation with the mother's wish.

It is important that appropriate critical care provision is the duty of the head of the institution when requested by the in-charge obstetrician.

SLCOG supports the clinical criteria for choice of critical care, as given in Table 4 of NICE guideline, June 25: 2019 (7), given below.

Clinical criteria for choice of critical care level

Level 3 care	Severe pre-eclampsia and needing ventilation
Level 2 care	Step-down from level 3 or severe pre-eclampsia with any of the following complications: • Eclampsia • HELLP syndrome • Haemorrhage • Hyperkalemia • Severe oliguria • Coagulation support • Intravenous antihypertensive treatment • Initial stabilization of severe hypertension • Evidence of cardiac failure • Abnormal neurology
Level 1 care	Pre-eclampsia with hypertension Ongoing conservative antenatal management of severe preterm hypertension Step-down treatment after birth

Care of woman after delivery

Continue monitoring of clinical parameters with the same vigilance in the first 48 hours following delivery of a patient who has been delivered. Medications used in pregnancy can be continued.

It is preferable the case is that of a preeclampsia urine albumin to be negative before discharge from the hospital. In patients with proteinuria persisting, discharge from the hospital for care in the community should be done by the consultant/specialist in charge of the care.

Drugs used in hypertension are excreted through breast milk, though no harmful effects are observed, manufacturers do not commit themselves on lactation. As preeclampsia settles down after delivery, by six weeks postpartum most medication can be tapered off and stopped with the individual assessment of patients. Providing appropriate contraceptive advice is recommended.

In Sri Lanka consideration should be for offering a permanent method of contraception to women who have completed their family or had experienced recurrent severe hypertension in pregnancy if cesarean delivery was contemplated as the mode of delivery.

The patients who had preeclampsia who were found to have no hypertension or proteinuria at 6 to 8 weeks postpartum could be reassured about their renal status as the absolute risk for End Stage Kidney disease is very low.

They can be assured that no further follow up on renal component or hypertension is necessary if they are in the normal range at 6 to 8 weeks. Hypertension persisting after 6-8 weeks from delivery should be referred for a medical specialists care.

Preeclampsia is a state where SLCOG recommends use of postoperative thromboprophylaxis with enoxaparin when operative delivery was the mode of delivery.

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