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“Under pressure…” An Anaesthetic Perspective of Hypertensive Disorders in Pregnancy

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TABLE OF CONTENTS

Background

Hypertensive disorders in pregnancy are encountered on a daily basis across the spectrum of our health care settings. Anaesthetists have a role to play in offering the women who present with these disorders the safest care possible for themselves, and their babies.

Hypertensive disorders remain a compelling contributor to maternal morbidity and mortality despite a declining trend in number of deaths as shown in the latest report published by the National Confidential Enquiries into Maternal Deaths (NCCEMD) Committee(1). Five-Hundred and ninety women died due to hypertensive disorders in the triennium 2017-2019, with eclampsia contributing 275 of those maternal deaths(1). This is less than in the previous triennium; but it remains a concern as, together with Obstetric Haemorrhage, Hypertensive Disorders in Pregnancy are a major direct cause of maternal deaths(1).

Seventeen percent of all maternal deaths in South Africa were attributed to hypertensive disorders in pregnancy(1). In contrast, the confidential enquiry in the United Kingdom revealed that 2% of the maternal deaths were due to hypertensive disorders in pregnancy(2). Moodley et al noted, from data shown in the preceding triennium, that nearly 75% of the maternal mortalities attributed to hypertensive disorders in pregnancy were thought to be potentially preventable, with the leading causes of death being cerebral haemorrhage and pulmonary oedema(3). The avoidable factors identified were inadequate assessment and diagnosis at Primary Health Care level; and poor adherence to standard protocols at regional, tertiary and central hospitals(3).

Classification of Hypertensive disorders in pregnancy

The categories for hypertensive disorders in pregnancy are described in the NICE guidelines as the following:

- Chronic Hypertension is hypertension which is present at or before 20 weeks of pregnancy. It may be primary or secondary(4)
- Gestational Hypertension is new-onset hypertension after 20 weeks' gestation, without proteinuria(4)
- Pre-Eclampsia is Gestational Hypertension with either **proteinuria** or other **maternal organ dysfunction**(4).

Maternal organ dysfunction involves renal, liver, neurological, haematological dysfunction or uteroplacental complications "such as foetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth"(4).

These categories are borne out in the South African guidelines as well, where there is also a consideration for 'pre-hypertension' where the measured blood pressure is elevated (BP 130-139/85-89), but does not meet criteria for the other hypertensive disorders(3).

The ISSHP includes the following as well:

- White-coat hypertension which refers to elevated blood pressures measured in the clinic/hospital, and normal blood pressures at home or work. This condition is not benign and confers an increased risk for preeclampsia(5)
- Masked hypertension is a blood pressure which is normal at the clinic/hospital visit and elevated at other times (most likely to be diagnosed by 24 hour ambulatory BP monitoring or automated home monitoring (5).
- Transient gestational hypertension occurs in the second or third trimester. An elevated blood pressure is detected in the clinic, but the subsequent readings settle to normal on the same-day repeat measurements(5).

The above come into play when patients present with the sequelae of a hypertensive disorder with severe features in particular(5).

Hypertension known before pregnancy or present in the first 20 weeks
Chronic hypertension
Essential
Secondary
White-coat hypertension
Masked hypertension
Hypertension arising de novo at or after 20 weeks
Transient gestational hypertension
Gestational hypertension
Preeclampsia* de novo or superimposed on chronic hypertension

*The term severe preeclampsia should not be used in clinical practice.

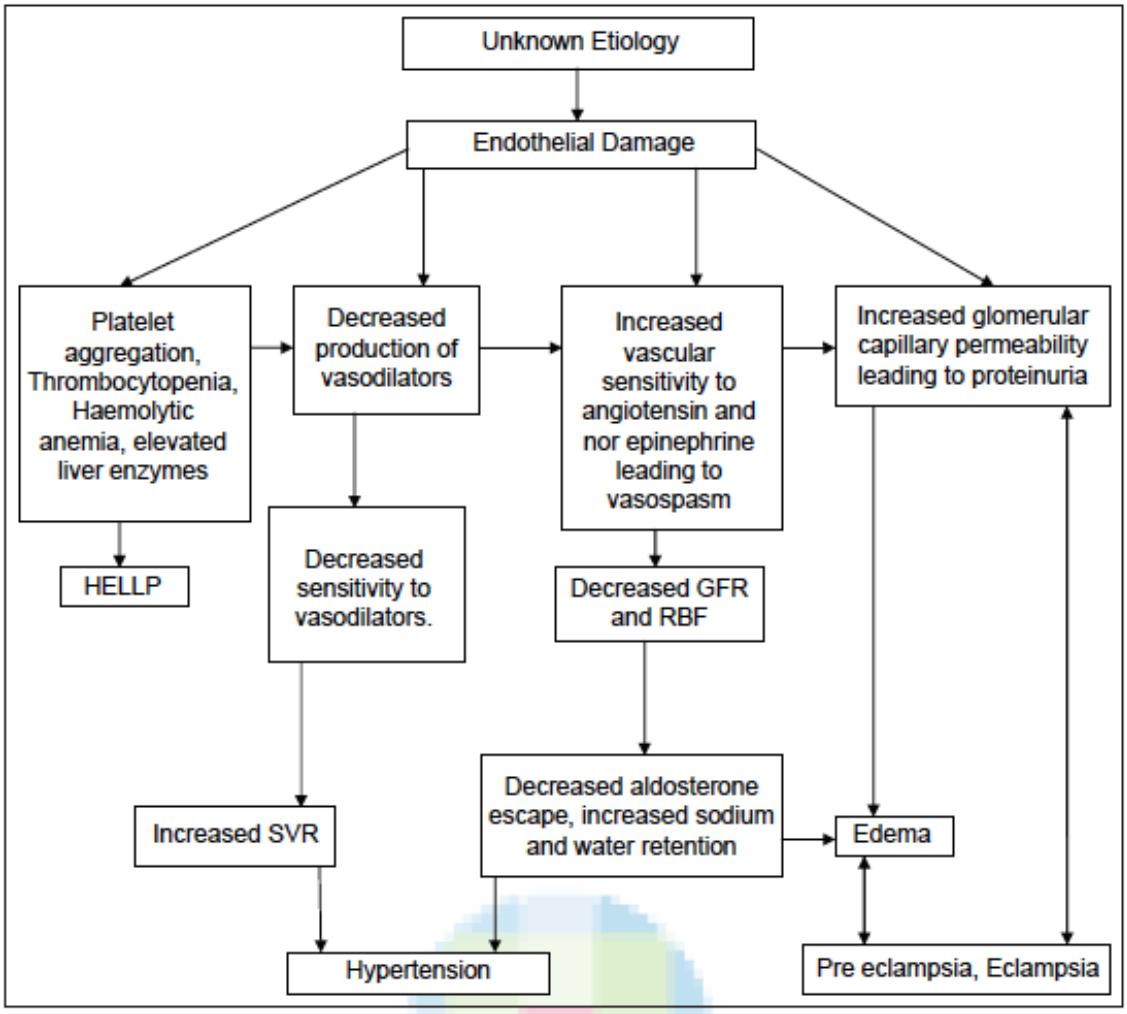
Hypertension, July 2018

Features of severity include headache, chest pain, epigastric pain/ discomfort, visual disturbances and eclampsia(3). Headaches may be from various causes, however, a new onset headache, in the presence of hypertension, should be considered to be part of preeclampsia until proven otherwise(5).

Haemolysis, elevated liver enzymes and low platelets are referred to collectively as HELLP syndrome(5). This syndrome signifies severity in the setting of preeclampsia(5).

Eclampsia, which is the new-onset of generalised, tonic-clonic seizures or coma, in a woman with preeclampsia remains one of the more serious manifestations of hypertensive disorders in pregnancy(6).

Pathophysiology



Anesthesia: Essays and Researches, Sep-Dec 2013

During normal pregnancy, hormonal fluctuations result in changes in the cardiovascular physiology of the parturient(7). Systemic vasodilation results from increases in oestrogen, progesterone and relaxin early in the first trimester; while plasma volume increases due to salt and water retention caused by an augmentation in the renin-angiotensin-aldosterone system(7). There is also an increase in stroke volume. The heart rate increases to compensate for the systemic vasodilation and physiologic anaemia (due to the red cell mass not rising in proportion to the plasma volume(7). There is an increase in cardiac output, owing to the increased stroke volume and heart rate, to compensate for the lower vascular resistance. This maintains the blood pressure necessary for perfusion of the placenta and other maternal organs(7).

Various theories have been proposed to explain the evolution of hypertension and preeclampsia. Among these are: “chronic uteroplacental ischaemia, immune maladaptation, very low-density lipoprotein toxicity, genetic imprinting, increased trophoblast apoptosis or necrosis, and an exaggerated maternal inflammatory response to deported trophoblasts”(8).

Preeclampsia is postulated to bring about vascular endothelial dysfunction due to decreased placental perfusion as a result of ineffective cytotrophoblastic invasion of the uterine spiral arteries(7). The placental hypoxia brings about a series of events which result in endothelial dysfunction(7). Lower concentrations of angiogenic factors such as vascular endothelial growth

factor and placental growth factor as well as higher levels of the placental soluble fms-like tyrosine kinase 1 are the angiogenic imbalances associated with the development of preeclampsia(7).

Poor placentation due to the syncytiotrophoblast stress is thought to cause early-onset preeclampsia; whereas late-onset preeclampsia is thought to be as a result of the placenta outgrowing its circulation(7).

De novo hypertension in the postpartum period may be due to fluid shifts (such as the mobilization of fluid into the intravascular space or administration of fluids), and/or the administration of vasoactive agents(7).

Risk Factors

Table 2 Strong and moderate risk factors for development of pre-eclampsia[7]

Strong risk factors	Moderate risk factors
Prior pre-eclampsia	Primiparity
Chronic hypertension	Primipaternity – changed paternity and inter-pregnancy interval >5 yrs
Maternal BMI >30	Advanced maternal age ≥40 yrs
Pregestational diabetes mellitus	Family history of pre-eclampsia
Antiphospholipid syndrome/ systemic lupus erythematosus (SLE)	Multiple gestation
Assisted reproductive therapies	Chronic kidney disease

BJA Education, October 2020

Diagnosis

The measuring of blood pressure is an important factor. In 1992, Cunningham and Lindheimer described using the Korotkoff phase V in most cases(9). The International Society for the Study of Hypertension in Pregnancy (ISSHP) notes that mercury sphygmomanometers are no longer widely available, and suggests crystal sphygmomanometers as an alternative; noting that aneroid devices may be inaccurate if not calibrated regularly and that any automated devices chosen should be shown to be reliable in both pregnancy and in preeclampsia(5). The South African Guidelines for Hypertensive disorders in pregnancy advocate for measurements using automated devices which have been validated in pregnant women, which are also regularly calibrated(3).

Special attention should be paid to ensure an accurate measurement is obtained. This involves, positioning the parturient appropriately, selecting the correct size cuff, and ensuring that the arm being used for measurement is free of clothing(3).

According to South African guidelines (as well as the NICE and ACOG statements), hypertension is defined as a systolic blood pressure of >140mmHg or a diastolic blood pressure of >90mmH(3, 4, 8).

South African guidelines specify that the blood pressure measurement should be repeated within 15 minutes if there are slight elevations or when systolic pressures between 140 and 150mmHg are obtained(3).

Those women whose blood pressures are borderline (135/85 – 139/89mmHg), and are considered low risk, should have their blood pressure repeated within 30 minutes – 2 hours, and if it remains borderline, should be asked to return within 3-7 days for review(3).

All parturients diagnosed with hypertension, in South Africa, should then also be investigated for features of severity by obtaining a Haemoglobin, Platelets, creatinine level as well as an ultrasound of the foetus(3).

Visual dipsticks are an easily accessible tool that can be used to test a clean-catch specimen for proteinuria as well as to rule out infection (by the absence of white blood cells and nitrites) as a cause of the proteinuria(3). Protein/creatinine ratio can also be used to assess the amount of protein; as this and the albumin:creatinine ration have both been shown to have high specificity and sensitivity(3, 10). South African guidelines still advocate the use of the 24 hour urine protein collection whereas the NICE guidelines now recommend that this not be used routinely as this method was found to be awkward for women and could also delay the identification of proteinuria(3, 4, 10).

Although tests for placental growth factor and the ratio of soluble fms-like tyrosine kinase 1 to placental growth factor are described internationally, the South African guidelines do not recommend their implementation at this time, although the reason for this is not specified.(3-5). The cost and access implications may be some of the reasons for this in our setting.

The terms ‘mild’ and ‘severe’ are no longer used to describe the severity of disease, with the ACOG moving towards a description of “preeclampsia with severe features”(2).

Complications

Eclampsia accounted for 590 (the majority) of maternal deaths due to hypertensive disorders in the last triennial, which is 17% of the total number of maternal deaths in the triennial(1).

Intracranial haemorrhage and cerebral oedema were the cerebral complications noted to be a cause of death in the assessment of the maternal mortalities due to hypertensive disorders(1). Pulmonary oedema (or cardiac failure) accounted for 35.1% of the maternal deaths due to hypertensive disorders(1).

Acute kidney injury, liver failure and disseminated intravascular coagulation were also counted among the final causes of death in the women with hypertensive disorders of pregnancy(1). Preeclampsia is associated with long term cardiovascular and metabolic effects in the woman even years after the pregnancy(1).

Management principles

Prevention

Aspirin

Aspirin prevents preeclampsia by reversing platelet aggregation which has been induced by an imbalance of thromboxane A2/prostacyclin ratio mediated by the endothelial dysfunction(7). The ISSHP recommendations advocate that low-dose (75-162mg/day) aspirin be commenced in those women with 'strong risk factors' before 20 weeks (ideally before 16 weeks) gestation(5).

The South African guidelines concur and go further to suggest that it should be started as early as 12 weeks for those women who 'book' early enough(3).

Table 1. Clinical Risk Factors and Aspirin Use*

Level of Risk	Risk Factors	Recommendation
High†	• History of preeclampsia, especially when accompanied by an adverse outcome	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
	• Multifetal gestation	
	• Chronic hypertension	
	• Type 1 or 2 diabetes	
	• Renal disease	
	• Autoimmune disease (ie, systemic lupus erythematosus, the antiphospholipid syndrome)	
Moderate‡	• Nulliparity	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors§
	• Obesity (body mass index greater than 30)	
	• Family history of preeclampsia (mother or sister)	
	• Sociodemographic characteristics (African American race, low socioeconomic status)	
	• Age 35 years or older	
	• Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)	
Low	• Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

*Includes only risk factors that can be obtained from the patient's medical history. Clinical measures, such as uterine artery Doppler ultrasonography, are not included.

†Single risk factors that are consistently associated with the greatest risk of preeclampsia. The preeclampsia incidence rate would be approximately 8% or more in a pregnant woman with one or more of these risk factors.

‡A combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk of preeclampsia. These risk factors are independently associated with moderate risk of preeclampsia, some more consistently than others.

§Moderate-risk factors vary in their association with increased risk of preeclampsia.

Modified from LeFevre, ML. U.S. Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2014;161(11):819–26.

Obstetrics & Gynecology, June 2020

Calcium

In studies as early as the 1950s, an association was shown between reduced rates of preeclampsia and eclampsia among those who consumed calcium-rich diets(7). Calcium supplementation is to be given to all local parturients, as per WHO recommendations, as South African women have been found to be calcium deficient(3, 7).

Statins

The pleiotropic antioxidant, anti-inflammatory, and antithrombotic effects of statins (with a specific focus on the effects on nitric oxide synthesis and antiangiogenic soluble Fms-like tyrosine kinase-1 expression) have been found to alleviate endothelial dysfunction in preclinical animal models(7). Promising results have been found in a small case series of preeclamptic women treated with pravastatin, however larger clinical trial are still underway(7).

Chronic treatment

The aim of controlling maternal blood pressures is to prevent intracerebral haemorrhage and stroke(2).

NICE guidelines recommend that target blood pressures in those on treatment is 135/85, while the ISSHP recommends maintaining the blood pressure in the range of systolic blood pressure 110 to 140 and diastolic blood pressures of 80 to 85; and the South African guidelines suggest aiming for blood pressures of less than or equal to 140/90(3-5).

Antihypertensives

Methyldopa

Methyldopa is the recommended first line agent by American, Canadian, European, Australian/New Zealander and South African guidelines, although it has been demonstrated to be inferior to calcium channel blockers and beta-blockers in preventing severe hypertension(3, 7). Methyldopa is also associated with fewer adverse infant outcomes(7).

Beta-blockers

The British guidelines recommend oral labetalol as the first line agent(7).
Other beta-blockers are less well studied, although Canada and Australia/New Zealand have included some agents in their first-line armamentarium(7).
The ACOG specifically advises against the use of atenolol as it is known to cause intrauterine growth retardation(7).

Calcium channel blockers

Dihydropyridine calcium channel blockers are used in most guidelines(7). Data for amlodipine is limited, but nifedipine is used almost universally(7).The Nice guidelines suggest nifedipine as a second-line oral agent for outpatient care, whereas South African guidelines recommend the use of oral nifedipine in the treatment of severe hypertension in the acute setting(3, 4).

Rescue/ Acute management of High BPs or features of severity

For blood pressures greater than or equal to 160/110, it is necessary to stabilise the woman and then to refer her for specialist care(3).
In cases where a woman is seen at a clinic or primary health care setting, and is found to have proteinuria, she should be referred to a hospital which is accredited for caesarean deliveries (3).
In those women found to have preeclampsia with features of severity, they should be referred up to a regional or tertiary hospital(3).

The process of stabilising a woman is described in the South African guidelines as follows:

- Inform receiving hospital (regional or tertiary).
- Start one IV line with 200 mL Ringer's lactate/or 200 mL normal saline (whichever is available); run IV line slowly, it is just for access.
- Start magnesium sulphate (4 g intravenous infusion (IVI) in 200 mL normal saline/Ringer's lactate over 20 minutes, plus 10 g intramuscular injection (IMI) (5 g in each buttock).[16,17]
- Reduce high blood pressure with 10 mg quick-acting nifedipine orally. This can be repeated every 30 minutes if the blood pressure does not drop below 160/110 mmHg. If the woman is unable to swallow, place the 10 mg nifedipine under the woman's tongue.
- Administer 1 g alpha-methyldopa orally.
- Insert a urinary catheter and monitor urine output every hour until the woman is transferred.
- Monitor the woman's BP, pulse and respiratory rate every 15 minutes until she is transferred.
- Emergency transfer ideally accompanied by an experienced nurse if available. Use the SBAR (Situation, Background, Assessment, Recommendation) form to provide the necessary information.
- Woman must be monitored and transferred in the **lateral position.**

SAMJ, Sep 2019

The foetus should only be monitored once the woman is stable, and the facility is able to offer her a safe delivery(3).

Anaesthetic implications

Although the ISSHP document does not specifically outline Anaesthetic considerations(5), several avoidable factors were identified as contributors to maternal deaths in the latest Confidential Enquiry into Maternal Deaths process, namely:
- Inadequate resuscitation
- Delay in diagnosing complications
- Poor postoperative care
- Inappropriate method of anaesthesia (11)

The anaesthetic team should be involved early in the care of the parturient with a hypertensive disorder in order to facilitate thorough preoperative evaluation and careful planning regarding the choice of analgesia and anaesthesia for labour(12). They may also be called up to provide critical care during hypertensive emergencies(2).

The main goals in the anaesthetic review involve assessing the severity of disease, performing an airway examination, evaluating the haemodynamic status of the patient, as well as excluding coagulation derangements which may preclude regional analgesia and/or anaesthesia(6).

Analgesia during labour

Central neuraxial analgesia during labour benefits women with preeclampsia with severe features by reducing the sympathetic response to pain and thereby facilitates cardiovascular stability(2). There is also the option to use the epidural catheter for operative delivery by administering a top up dose(2). A platelet count withing the last 6 hours (or more recent in those with HELLP syndrome or DIC) should be obtained prior to performing a neuraxial block(2). When neuraxial analgesia is contraindicated, inhalational and/or parenteral analgesia may be used, with patient-controlled analgesia providing a good alternative to regional analgesia(2).

Caesarean Delivery

Pre-operative (including risk stratification)

Risk prediction tools have been validated for use in this population to aid in earlier diagnosis and to improve outcomes by guiding management decisions. Various factors are incorporated and evaluated including placental biomarkers, uterine artery Doppler measurements and maternal risk factors(2). The PREP-S (Prediction model for Risks of complications in Early-onset Pre-Eclampsia [survivor analysis model]) and fullPIERS (Pre-eclampsia Integrated Estimate of Risk) are based on gestational age, vital signs and biochemical parameters(2). The fullPIERS can be applied at any gestation, whereas the PREP-S is only applicable up to 34 weeks' gestation(2). The other limitation is that the fullPIERS was validated in a high-resource setting, which may not be applicable in our setting. The miniPIERS was subsequently developed for use in low-resource settings(13).

Intra-operative

Anaesthetic plan

Regional anaesthesia is the modality of choice for caesarean deliveries, if there are no contraindications(2, 3, 6). Spinal, epidural or combined spinal epidural can all be utilised with good effect(2).

General anaesthesia is recommended if no platelet count is available or if the platelet count is less than 75 000 x 10^9 in the last 6 hours according to the South African guidelines(3). These guidelines also give room for discussion. If a specialist anaesthetist is directly involved in managing the case and pencil point spinal needles are available, then the cut-off may be considered at the lower level of 50 000 x 10^9, especially if the airway poses potential difficulty(3).

General anaesthesia is associated with the potential for difficult airway, the risk of aspiration, as well as the risk of marked increases in blood pressure at intubation and emergence(2, 8).

If a general anaesthetic is conducted, the intubation and extubation responses should be attenuated using magnesium and/or opiates for the former, and lignocaine for the latter(3).

Pharmacology

A 'recipe' to blunt the intubation response is suggested by Hawkins et al as the following:

- Lignocaine 1 – 1.5mg/kg IV at induction
- Labetalol 10mg boluses titrated up to 1mg/kg prior to induction
- Esmelol 2mg/kg IV (or 1mg/kg with lignocaine)
- Nitroglycerine 1.5 to 2.5mcg/kg IV
- Nicardipine 15 to 30mcg/kg IV (or 100 to 200 mcg bolus at induction)
- Fentanyl 1 to 3mcg/kg IV(6)

Multimodal analgesia should be employed for intra and post-operative pain management, including local anaesthetics infiltration, nerve blocks, paracetamol and opiates(3, 6). Non-steroidal anti-inflammatory agents(NSAIDS) are not recommended in the South African guidelines and by the ISSHP for preeclamptic women, however, the ACOG recommends that they should be used preferentially over opioid analgesics, as no differences in blood pressure, antihypertensive requirements or other adverse events were described in postpartum preeclamptic patients on magnesium who were managed with NSAIDS in the postpartum period(3, 5, 8).

Magnesium has significant implications for anaesthesia, however, it should be continued throughout the caesarean delivery, if a woman is on an infusion for seizure prophylaxis(2, 3, 8). Magnesium potentiates the action of non-depolarising neuromuscular blocking agents (NDNMBAs), but does not affect the actions of suxamethonium or sugammadex; therefore, if needed, small doses of NDNMBAs can be used, or an intubating dose of rocuronium may be used, if sugammadex is available(2).

Airway management

A rapid sequence induction and intubation are usually performed(6). Generalised airway and subglottic oedema, as well as the risk of mucosal bleeding, makes the airway, of a parturient with preeclampsia or eclampsia, challenging(2). The use of video-laryngoscopy is recommended by Goddard et al(2). Smaller endotracheal tubes should also be at hand in case of subglottic oedema(2).

Monitoring

Standard SASA monitors are mandatory for all cases. Invasive arterial pressure monitoring is not routinely indicated, unless there is haemodynamic lability and/or the use of intravenous vasoactive agents, as well as for frequent sampling in the setting of pulmonary oedema(2, 3). Central venous access is also not required routinely, and the insertion thereof should not delay care(2). There is no indication to insert a central venous or pulmonary artery catheter which is unique to preeclampsia(12).

Echocardiography is not routinely described in this population in both local and international guidelines. This may be due to poor access to the modality in lower resource settings. The number of skilled practitioners is also not optimal in all settings, although this should continue to change in the months and years to come.

Fluids

Preloading is not recommended; with fluid restriction or goal-directed fluid therapy being advocated in the South African guidelines(3). Fluid balance should aim for euvolaemia, with the ISSHP recommendation of limiting fluids to 60-80 ml/hr to avoid pulmonary oedema, unless there are ongoing fluid losses(2, 5).

Management of the third stage of labour

Ergometrine should be avoided as it may precipitate a hypertensive emergency(2).
Oxytocin should be administered at a reduced infusion rate(3). (Beware the patient also receiving a magnesium infusion as the total fluid infusion rate may become very high if the oxytocin is not administered at a reduced infusion rate). This may necessitate a higher concentration of oxytocin in order to deliver the required amount at a lower infusion rate.

Post-operative

All patients should be managed in an acute-care setting, in consultation with the Obstetrician(3). This facilitates the close observation and acute management of blood pressures as well as allowing the monitoring for adverse events such as the development of pulmonary oedema and/or other features of hypertensive emergencies(2).

If an epidural catheter was inserted for labour analgesia or as an anaesthetic for caesarean delivery, its removal also bears the risk of causing an epidural haematoma in the patient with thrombocytopaenia(12). In the setting of thrombocytopaenia, a rising and acceptable platelet count should be seen prior to the removal of the catheter, which usually occurs within 2 – 3 days, but may take as long as 5-6 days in women with HELLP syndrome(12).

Magnesium for seizure prophylaxis should be continued for 24hours after the last seizure or delivery, whichever occurs first(12).

Conclusion

Hypertensive disorders may affect many systems in the pregnant woman; and require the careful and vigilant attention of a multidisciplinary team. The various guidelines available provide ample instructive details for the prevention, diagnosis and management of these women. In all settings, the use of the available resources appropriately can decrease the morbidity and mortality seen as a result of hypertensive diseases in pregnancy.

Anaesthetic teams should work together with obstetric colleagues to control blood pressure, control and prevent further seizures, manage airways safely, provide labour analgesia (and anaesthesia for caesarean delivery), while preventing major complications.

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