Hypertension is the most common medical complication encountered during pregnancy, complicating 5-15% of all pregnancies.\(^{(1,2)}\) In a systematic review, Abalos, et al. reported upon global and regional estimates of pre-eclampsia and eclampsia from 40 countries. Their model gave an estimated incidence of 4.6% and 1.4% for pre-eclampsia and eclampsia respectively, but they noted wide variations across regions.\(^{(3)}\)

With the increasing prevalence of obesity and diabetes as well as the trend to more advanced age at childbirth in many countries, the rates of pre-existing (chronic) and pregnancy-induced hypertensive conditions such as pre-eclampsia seem set to rise even further.\(^{(4)}\)

The impact of hypertensive diseases on pregnancy is certainly important from both maternal and fetal perspectives during pregnancy and even thereafter. The maternal mortality associated with these conditions remains high in both developed\(^{(5)}\) and developing countries.\(^{(6,7)}\) In South Africa, a legislated confidential enquiry process has facilitated the expert assessment of all maternal deaths since 1999. The category of “hypertensive disorders in pregnancy” has consistently remained an important primary cause of death. During the 2008-2010 triennium, hypertensive disorders during pregnancy accounted for 14% of all maternal deaths in South Africa. This figure represented a continued decrease from 19% in 2002-2004 and 16% in 2005-2007. In the most recent triennium there were 679 deaths reported in the hypertension category. Of these, 5% were due to chronic hypertension and the rest due to pre-eclampsia including superimposed and complicated pre-eclampsia. Amongst these women, pulmonary oedema (28%), intracranial haemorrhage (23%), cerebral oedema resulting in coning (9%) and brain death following a hypoxic event (7%) were the most frequently recorded final causes of death.

Although most of these deaths occurred in tertiary and regional hospitals, hypertensive deaths still comprised 15% of all maternal deaths at Community Health Centres, emphasising the importance of correct initial management at all levels of care.\(^{(6)}\)

With regards to the timing of the emergency event related to hypertension, 28% \((n=191)\) occurred in the post-partum period. An important aspect of the Saving Mothers report is the attention paid by assessors to avoidable factors, missed opportunities and sub-standard care. In the most recent report, health worker orientated emergency management problems were noted in 42% of hypertensive deaths at Community Health Centres and District hospitals, 33% at Regional hospitals and 17% at Tertiary hospitals.\(^{(8)}\) Not only is the mortality associated with hypertensive disorders in pregnancy high, but these conditions are a frequent source of significant morbidity.\(^{(8,9)}\) Cases with Severe Acute Maternal Morbidity (SAMM) share many characteristics with maternal deaths.\(^{(10)}\)

Therefore understanding and managing SAMM also helps to decrease or prevent maternal mortality.
From the fetal and neonatal perspective, hypertensive diseases of pregnancy remain important causes for delivery of very low birthweight babies, preterm births (with the risk of intracerebral haemorrhage) and perinatally related losses, that are often caused by placental abruption and/or intra-uterine growth restriction. The perinatal outcomes of the 679 hypertensive maternal deaths that occurred in the 2008-2010 triennium in South Africa included 144 (2.1%) stillbirths and 18 (2.7%) neonatal deaths, while 226 (33.3%) of the women died undelivered.

Anti-hypertensive therapy is used in the acute and non-acute clinical scenario. With regards to the non-acute management of the hypertensive diseases of pregnancy, Rubin, in 1986, noted a shift away from non-pharmacological management regimens, such as bed rest or early delivery, towards the introduction of anti-hypertensive agents with a view to useful prolongation of pregnancy. Clinicians using anti-hypertensive agents during pregnancy have to balance both the benefits and the risks of such therapy while considering maternal and fetal interests. Although a wide variety of agents have been used, few have been subject to controlled clinical trials, due to concerns harboured by health research ethics committees and pharmaceutical companies. The result is that many medications are prescribed off-label in doses and frequencies extrapolated from research in non-pregnant subjects with a very different physiology. This problem is particularly applicable to anti-hypertensive agents and remains an ethical conundrum.

**PHYSIOLOGY**

Several important physiological changes occur during normal and even complicated pregnancies. It is well known that blood pressure is directly proportional to systemic vascular resistance and cardiac output. Starting early in the first trimester and peaking around the 28th week of gestation, the plasma and red cell volumes increase by 40% and 25% respectively. The greater increment in plasma volume gives rise to the physiological anaemia of pregnancy. Cardiac output increases by 40% during pregnancy and a further 20% during labour. Apart from the plasma volume expansion, there is vasodilatation leading to a fall in blood pressure during the second trimester of pregnancy. This is due to several factors that include vascular refractoriness to angiotensin II, as well as increased production of endothelial prostacyclin and nitric oxide. The nadir in systolic and diastolic pressure is reached at about 22-24 weeks’ gestation. Thereafter there is a steady rise to pre-pregnancy levels at term. Immediately after delivery, blood pressure usually falls and then rises again up to the third or fourth day postpartum. The physiological lowering of blood pressure in the second trimester may obscure the diagnosis of mild chronic hypertension in women without the benefit of pre-pregnancy check-ups and who only book for antenatal care in the second trimester. When blood pressure remains elevated beyond 12 weeks after delivery, the diagnosis of chronic hypertension is confirmed.

**CLASSIFICATION**

There are several classification frameworks for hypertension in pregnancy, some being more complex than others. Steegers, et al. have summarised the main differences between classifications as: inclusion of non-proteinuric pre-eclampsia; differentiation between research and clinical definitions; the acceptance of early pre-eclampsia as severe; the definition of severe pre-eclampsia and the importance of white-coat hypertension. The classification of hypertension in pregnancy of the International Society for the Study of Hypertension in Pregnancy (ISSHP) is in the final stages of review but key aspects of their current classification are shown in Table I.

While most classifications use fixed thresholds it is still recommended that a pregnant woman with a rise in sBP ≥30mmHg or dBP ≥15mmHg should be carefully monitored. As seen in Table I, hypertension in pregnancy can be broadly divided into conditions of pre-existing hypertension, pregnancy-induced hypertension (gestational hypertension) and pre-eclampsia that manifest clinically after 20 weeks’ gestation. Some women will not have been diagnosed with chronic hypertension but

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**TABLE 1: Key aspects from the classification and diagnosis of the hypertensive disorders of pregnancy by the International Society for the Study of Hypertension in Pregnancy (ISSHP).**

<table>
<thead>
<tr>
<th>Definition of Hypertension in Pregnancy</th>
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<tr>
<td>A systolic blood pressure (sBP) ≥140mmHg and or a diastolic (dBP) ≥90mmHg (K5) respectively.</td>
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<table>
<thead>
<tr>
<th>Classification</th>
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<tr>
<td>Four categories: pre-eclampsia, gestational hypertension, chronic hypertension (essential and secondary), and pre-eclampsia superimposed on chronic hypertension. The definitions are listed.</td>
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</table>

<table>
<thead>
<tr>
<th>Pre-eclampsia: The clinical diagnosis is as follows:</th>
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<tr>
<td><strong>De novo hypertension</strong> after gestational week 20, and new onset of one or more of the following</td>
</tr>
<tr>
<td>Proteinuria (&gt;300mg/day or a spot urine protein/creatinine ratio &gt;30mg/mmol)</td>
</tr>
<tr>
<td>Renal insufficiency (creatinine &gt;90μmol/L or oliguria)</td>
</tr>
<tr>
<td>Liver disease (raised transaminases and/or severe right upper quadrant or epigastric pain)</td>
</tr>
<tr>
<td>Neurological problems: convulsions (eclampsia), hypertreflexia with clonus, severe headaches with hypertreflexia, persistent visual disturbances (scotoma)</td>
</tr>
<tr>
<td>Haematological disturbances: thrombocytopenia, disseminated intravascular coagulation, haemolysis</td>
</tr>
<tr>
<td>Fetal growth restriction.</td>
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</table>

Normalisation of blood pressure within 3 months postpartum.

<table>
<thead>
<tr>
<th>Gestational Hypertension:</th>
<th>De novo hypertension alone, appearing after gestational week 20.</th>
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</table>

<table>
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<tr>
<th>Chronic Hypertension:</th>
<th>Presence or history of hypertension preconception or in the first half of pregnancy. Considered “essential” if there is no underlying cause or “secondary” if associated with definitive etiology.</th>
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</table>

<table>
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<tr>
<th>Pre-eclampsia superimposed on chronic hypertension:</th>
<th>Development of new signs and/or symptoms associated with pre-eclampsia after gestational week 20, as above, in a woman with chronic hypertension.</th>
</tr>
</thead>
</table>
HYPERTENSION DURING PREGNANCY

if hypertension is noted before 20 weeks' gestation, it is likely to be a pre-existing problem. In such cases secondary causes e.g. renal, cardiac and endocrine should be excluded before a diagnosis of essential hypertension is made. Women with chronic hypertension are at increased risk of developing super-imposed pre-eclampsia. Pre-eclampsia is a pregnancy specific and particularly dangerous condition with multifactorial etiology that is generally characterised by new onset hypertension and proteinuria after 20 weeks' gestation. Pre-eclampsia may be complicated by eclampsia (grand mal convulsions), blindness, pulmonary oedema, haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, renal failure, placental abruption, intra-uterine growth restriction (IUGR) or intra-uterine death (IUD) of the fetus. A detailed discussion of pre-eclampsia is however beyond the scope of this article. Apart from the problems of pre-eclampsia, any form of severe hypertension is dangerous due to the association with stroke, end-organ damage and placental abruption(121).

DIAGNOSING HYPERTENSION AND TREATMENT GOALS

The Millennium Development Goal number 5 requires a specific reduction of maternal mortality by 2015. When one considers the number of hypertensive deaths occurring annually in South Africa, it is clear that the identification of hypertension during pregnancy as well as treatment towards the prevention and management of hypertensive crises will help towards achieving this laudable goal. The implementation of clinical guidelines for treatment and referral of pregnant women with hypertension has been shown to reduce maternal and perinatal risk.(22)

General antenatal care (history, checking blood pressure and urine) is largely directed toward the screening and detection of hypertension and pre-eclampsia which may be asymptomatic in the early stages. Blood pressure should be measured as it is done outside of pregnancy with the patient at rest, sitting upright, arms supported and the cuff at the level of her heart. When measured in the recumbent position, the patient should lie on her side, again with the cuff at the level of her heart. Korotkoff V sounds should be used to define diastolic blood pressure. Obesity is a problem and “large” cuffs should be used when the circumference of the upper arm is ≥33cm. Another matter to consider is the device used to measure blood pressure. The mercury sphygmomanometer has been the gold standard but has been removed from many hospitals and clinics due to safety concerns. The replacement devices are generally aneroid and automated machines, but only a few of the automated blood pressure measuring devices on the market have been validated for use in pregnancy. The lower threshold for diagnosing hypertension is generally agreed upon (see Table I) but the definition of severe systolic hypertension (160mmHg or 170mmHg) is still debated due to concerns about lethal maternal stroke.(1921) At Tygerberg Academic Hospital, severe hypertension in pregnancy is defined as systolic blood pressure (sBP) ≥160mmHg or diastolic blood pressure (dBP) ≥110mmHg. Non-severe hypertension is defined as sBP 140-159mmHg and dBP 90-109mmHg. Parenteral antihypertensive therapy may be necessary to control acute severe hypertension but this can be followed by oral maintenance therapy.

There is currently no universally accepted standard of care although there is broad agreement on the principles of assessment, surveillance, management of severe systolic and diastolic blood pressures, prevention and treatment of eclampsia and avoidance of aggressive rehydration in pre-eclampsia. In contrast to the non-pregnant scenario, therapy for moderate hypertension in pregnancy or pre-eclampsia is controversial. This is because women with mild, uncomplicated hypertension without end-organ involvement are at lower risk of adverse outcomes over the “short period” that pregnancy represents.(22) Due to the mid-trimester fall in blood pressure, it may be appropriate to stop anti-hypertensive medication in uncomplicated pre-existing hypertension, only re-instating it if required. Many physicians will still treat non-severe hypertension in pregnancy in order to reduce the risk of severe hypertension and maternal end-organ damage when the blood pressure rises above 150/100mmHg, but this has not been shown to decrease super-imposed pre-eclampsia.(122) Systolic blood pressure is now regarded as the strongest predictor of maternal end-organ damage.(21) With prolonged treatment of non-severe hypertension, fetal growth restriction due to placental hypoperfusion remains a concern, hence the importance of fetal surveillance. A Cochrane review of 46 trials, including 4 282 women, concluded that it remains unclear whether antihypertensive drug therapy for mild/moderate hypertension in pregnancy is worthwhile.(25)

While therapy for moderate hypertension or pre-eclampsia is controversial, it is well accepted in the severe form as severe hypertension is associated with more adverse outcomes.(18) However, because the placenta functions as a low resistance shunt without autoregulation, lowering the blood pressure too rapidly or too far is detrimental to the fetus. In the acute phase, the aim is an initial reduction of 25% in the first hour, followed by further reduction over hours to values below 160/110mmHg. Thereafter, the target range is 140-155sBP/90-105dBP. A summary of the treatment thresholds and targets of 5 societies is provided by Vest and Cho. (1) In severe hypertension or severe pre-eclampsia the primary purpose of therapy is not to change the course of the illness but to prevent cerebral haemorrhage and hypertensive encephalopathy. Thus the initial focus for the benefit of therapy is directed towards the safety of the mother. It is now known that the fetus too can benefit from such therapy when it allows the careful continuation of pregnancy remote from term. Regarding severe pre-eclampsia, 2 randomised controlled trials have shown that expectant management of early onset, severe pre-eclampsia is of benefit to premature fetuses.(2627) These and other studies...
have shown that perinatal outcome can be directly linked to gestation at delivery. (24) Very preterm delivery is associated with the significant risks of pulmonary immaturity and the development of neurocognitive compromise. The administration of betamethasone to enhance fetal pulmonary maturity and decrease fetal intraventricular haemorrhage and necrotising enterocolitis, together with a short but significant prolongation of pregnancy, can greatly improve the neonatal outcome. Due to the fact that approximately 2 weeks of gestation can be gained by expectant management, oral rather than parenteral therapy is the appropriate choice for this longer period of therapy. When anti-hypertensive medications are used to control blood pressure and postpone delivery in pre-eclampsia with the goal of improving fetal outcome, this is only a palliative step and the disease process itself is not modified. The timing of delivery and balancing of the maternal and fetal risks remains a critical decision.

The care of pregnant women with hypertension does not end with delivery. Hypertension caused by pre-eclampsia usually resolves within a few days of delivery and returns to baseline by 12 weeks postpartum. (1) During the post-partum period many women will require ongoing control of hypertension with oral agents. Labetalol, nifedipine, enalapril and captopril are safe during lactation but other ACE inhibitors and angiotensin receptor blockers should not be prescribed. (29) For women who entered pregnancy with normal blood pressure it is generally recommended to discontinue antihypertensive medications 3–4 weeks after delivery and then to observe blood pressure at regular intervals for one month and then yearly thereafter. (1)

Recently, compelling evidence associating hypertensive disorders in pregnancy with cardiovascular risk factors, has been presented. (20) A very large study from Norway (21) together with others from around the world offer plausible evidence that women who experienced pregnancy-related hypertension are at elevated risk for hypertension and metabolic disorders such as non-insulin dependent diabetes mellitus later in life. (30,32) Although it is still uncertain whether the associations between pregnancy hypertension and subsequent chronic disease are due to common pre-existing conditions or by the direct effect of the complication during pregnancy, the former hypothesis is currently thought to be more likely. (6) This debate should however not delay the implementation of simple measures aimed at improving long-term outcomes such as smoking cessation, diet, management of obesity, exercise programmes and regular checking of blood pressure, lipid and glucose profiles. Cardiologists in particular should take note of these associations.

### Anti-hypertensive agents

The management of pregnant women with hypertension is based on the following principles:

- Exclude or confirm pre-eclampsia after 20 weeks' gestation.
- Treat the hypertension.
- Fetal surveillance.
- Decide on timing and type of delivery.

In this section only the third principle will receive detailed attention but readers are encouraged to read more widely, particularly regarding pre-eclampsia. Regardless of the underlying pathology, severe hypertension merits treatment in its own right, because when the mean arterial pressure rises above 150 there is loss of cerebral auto-regulation and a risk of cerebral haemorrhage. However, in pre-eclampsia cerebral complications can occur without very high blood pressure as blood pressure does not always correlate with auto-regulation functionality. (33) As stated in the introduction there are insufficient randomised trials to direct the optimal treatment of hypertension in pregnancy, thus physicians should use the agent with which they feel most comfortable. (19)

### Hypertensive emergencies

Therapy for acute severe hypertension is essential. The primary purpose of therapy is not to change the course of the illness but to prevent cerebral haemorrhage, hypertensive encephalopathy, acute renal or cardiac failure, arrhythmias or placental abruption. Although the initial focus on the benefit of therapy is directed towards the safety of the mother whose well-being takes priority in the acute phase, the fetus too benefits from such therapy, particularly when it allows the careful continuation of pregnancy remote from term. If the reduction in blood pressure is too rapid, this may lead to inadequate uteroplacental blood flow. A fast but smooth and controlled reduction is the ideal. Careful fetal monitoring to detect fetal distress is required but maternal well-being takes priority in the acute phase. Women with acute severe hypertension should be stabilised and transferred to, or managed in a high-care dependency unit. Physicians should be aware that automated oscillometric devices may underestimate blood pressure. (25) Women with pre-eclampsia and acute severe hypertension have a reduced intravascular volume and require pre-treatment with a small volume of fluid e.g. 250ml crystalloid fluid before or during administration of anti-hypertensive medication. (16) The following agents are commonly used. Drug safety classes are shown in Table 2.

- Nifedipine (Class C) 5mg or 10mg (short-acting capsule) swallowed. Note: In the pregnant patient the capsule should not be bitten or administered sub-lingually. A rapid effect on the blood pressure can still be anticipated. It may be repeated every 30 minutes as needed. Nifedipine should be avoided in women with known atherosclerotic cardiovascular disease, a long history of diabetes (>15 years) or >45 years of age due to the risk of sudden cardiac death. (37)
Dihydralazine (Class C) Mix one ampoule with 20ml sterile water. Administer 2ml (2.5mg) boluses intravenously every 20 minutes until blood pressure is <160/110mmHg. When the patient is ready for transfer; administer 6.25mg intramuscularly. It has been associated with more side-effects than other rapid-acting agents. 

Labetalol (Class C) When maternal tachycardia accompanies acute severe hypertension labetalol is a good option. A 20mg intravenous bolus followed by 40mg if not effective within 10 minutes; then 80mg every 30 minutes to a maximum total dose of 220mg. It may also be used as a continuous infusion.

Magnesium sulphate (MgSO4) (Class B) This drug is not an anti-hypertensive agent but is used for the treatment and prevention of eclampsia in the acute scenario. A 4g intravenous loading dose over 15 minutes is followed by an infusion of 1g/hour.

The aim here is not to normalise the blood pressure, but rather to reduce the pressure to levels associated with a decreased risk of vascular accidents. In the acute scenario, the aim is to reduce the sBP/dBP to <160/110mmHg while recording the blood pressure every five minutes until stable. In a meta-analysis investigating treatment for severe hypertension in pregnancy, Magee, et al. concluded that hydralazine lacked support as a first line agent and that nifedipine and labetalol showed promise. In 2013 a small randomised controlled trial comparing oral nifedipine to intravenous labetalol for hypertensive emergencies in pregnancy showed nifedipine to be superior. Following control of severe hypertension, oral maintenance therapy should be instituted or increased.

Oral maintenance therapy

The commonly considered agents are briefly discussed below. The ideal agent for use during pregnancy should have the following characteristics: ease of administration, rapid onset of action, controlled lowering of blood pressure, a sustained duration of action, maintenance of placental blood flow and lack of serious side effects for the mother and fetus. Classes of agents may be combined when maximum doses are inadequate to achieve the desired blood pressure goals. An increasing body of evidence suggests that maternal hypertensive diseases during pregnancy are associated with adverse neurocognitive outcomes in children. It is therefore difficult to separate the effects of the disease and the therapy but evidence suggests that methyldopa, labetalol and nifedipine are the safer agents.

Methyldopa (Class B), which acts as a false neurotransmitter in the central nervous system is widely regarded as the first choice agent during pregnancy. It has no effect on the cardiac output. Importantly, it has been prospectively evaluated in randomised clinical trials and has been shown to be safe for the mother, neonate and infant. Unfortunately methyldopa has only mild potency with a low oral bioavailability and a slow onset of action. Sedation and depression are both recognised side effects when high doses are used. It should therefore be avoided in the postpartum period. The typical dosage starts with 250mg 8-hourly, increased as necessary to a maximum of 750mg 8-hourly. When a second agent is needed to control maternal blood pressure the patient should be referred to an institution with specialist care.

Nifedipine (Class C), is a widely used calcium channel blocking agent. The use of nifedipine in pregnancy has been fairly well investigated. A number of randomised controlled trials have shown nifedipine to be an effective anti-hypertensive agent. It has been used for acute and maintenance therapy, moderate and severe degrees of hypertension and for chronic as well as pregnancy induced conditions. A useful attribute of nifedipine is that the degree of reduction in blood pressure it produces appears to be directly proportional to the pre-treatment pressure. It should be noted that with regards to uteroplacental perfusion, the normotensive situation differs substantially from pre-eclampsia. In normal pregnancies the uterine spiral arteries are converted to uteroplacental arteries by trophoblast invasion. Thus their muscular components are lost and a low-resistance/high-flow system is formed. In pre-eclampsia this fails to occur completely and uteroplacental flow is reduced. So, while calcium channel binding agents have little direct effect on the normal uteroplacental bed, they may be able to exert a direct vasodilatory effect in pre-eclampsia, because of the partial preservation of the muscular component of the arteries. A study reporting on in-utero exposure to nifedipine and the development of children up to the age of 18 months shows the agent to be safe.

Other reported benefits of calcium channel blockers include their rapid onset of action after oral administration, inhibition of platelet aggregation, decrease in erythrocyte
aggregation,(48) improved renal function(49) and increased urinary excretion of prostacyclin metabolites.(50) Despite causing vasodilation, these agents seldom cause a problematic tachycardia. Transient facial flushing, headaches and warm sweaty extremities seem to be the most common side effects. The typical dosage starts with 30mg (slow release formulation) daily or 12-hourly as necessary, to a maximum of 120mg daily.(51) The combination of a calcium channel blocker and MgSO4 has been shown to be safe.(52)

β-adrenergic blocking agents e.g. atenolol (Class D). The mechanism of action involves a reduction in cardiac output, a central adrenergic effect and a blockage of renin secretion. These agents may cause fetal intra-uterine growth restriction (IUGR) and neonatal hypoglycaemia, but may be used in the postpartum period. Labetalol (Class C) is a unique adrenoceptor antagonist as it has both α-1 and non-selective β-blocking effects. It lowers blood pressure without compromising the maternal cardiovascular system by producing peripheral vasodilation. β-blockers should be avoided in patients with asthma and congestive heart failure. The dose of oral labetalol begins at 200mg 12-hourly, increasing to a maximum of 1 200mg constituted in 2-3 divided doses.

Hydralazine (Class C), acts directly on the vascular wall producing vasodilatation. When administered orally the effect is weak.

Diuretics e.g. hydrochlorothiazide (Class B). The use of these agents during pregnancy is controversial, largely due to the volume depletion associated with pre-eclampsia. Their use should be limited to women with early, severe chronic hypertension.

Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers and direct renin inhibitors (all Class D), are contra-indicated in pregnancy as they have been linked to complications throughout pregnancy including congenital anomalies, IUGR, oligohydramnios and perinatal renal failure.(50) Enalapril and captopril may be used with safety during lactation.

With oral maintenance therapy the majority of patients are controlled on methyldopa, and/or nifedipine. In problematic cases labetalol is useful.

CONCLUSION

There is no doubt that clinicians managing pregnant patients must have a thorough understanding of the management of hypertension. The choice of agents will vary according to the clinical situation but each clinical decision must be underpinned by knowledge of the agent to be used as well as the risks and benefits of such therapy to both the mother and the fetus or newborn infant.

Conflict of interest: none declared.

REFERENCES

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