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Therapeutics and anaesthesia

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Many aspects of hypertension care outside pregnancy may be applied in pregnancy, but little information is available on which to base decision-making. It would seem reasonable to continue previous dietary salt restriction and physical activity in women with pre-existing (and controlled) hypertension, encourage a heart-healthy diet in all women with a hypertension disorder of pregnancy, and take patient preference into account when deciding on place of care. Although bed rest has become a key part of obstetric practice and for care of women with a hypertension disorder of pregnancy, in particular, the evidence is lacking to support this practice. This may also increase thromboembolic risk. Antihypertensive treatment is strongly advised for women with severe hypertension. The most common agents are parenteral labetalol, hydralazine, or oral nifedipine capsules. Clinicians should familiarise themselves with multiple agents. Until the role of antihypertensive treatment for non-severe hypertension in pregnancy is clarified by ongoing research, clinicians should explicitly state an individual patient's blood pressure goal, which could reasonably be anywhere between 130/80 and 155/105 mmHg. Labetalol and methyldopa are used most commonly. Breastfeeding should be encouraged. Many risk factors for hypertension (e.g. obesity), as well as hospitalisation and pre-eclampsia, all increase the thromboembolic risk for pregnant women, and care providers should consider throm

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boprophylaxis in the appropriate setting. Finally, anaesthetists play a critical role in the management of women with a hypertension disorder of pregnancy, and should be involved earlier rather than later in the course of their care.

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Introduction

The management of women with a hypertensive disorder of pregnancy (HDP) involves more than management of the hypertension. Women with pre-existing hypertension or gestational hypertension, particularly with onset at less than 34 weeks' gestation, are at substantial risk of pre-eclampsia (i.e. up to 35%). Pre-eclampsia is a disorder of systemic endothelial cell dysfunction and, as such, care providers must provide comprehensive maternal and fetal surveillance.

In this chapter, we will review the effectiveness of practices traditionally applied to women with hypertension outside pregnancy, many of which are also used in pregnancy, namely dietary and lifestyle change, as well as antihypertensive treatment. Issues of particular relevance to women with pre-existing hypertension in pregnancy will also be considered as will thromboprophylaxis. Aspects of care related to anaesthesia and fluid management is applicable to all women with a HDP. Other chapters in this issue of *Best Practice and Research Clinical Obstetrics and Gynaecology* will cover areas of particular relevance to women with gestational hypertension or pre-eclampsia (see chapter on expectant versus temporising management of pre-eclampsia) and postpartum care and long-term maternal health (see chapter on postpartum evaluation, recurrence risk, and implications for long-term health).

Dietary and lifestyle changes

In the general population, non-pharmacological approaches to managing hypertension are encouraged and considered complementary to drug treatment. However, the short time frame for intervention in women with one of the HDP has meant that non-drug measures have been largely ignored in hypertension research. Greater understanding of the pathogenesis and physiology of HDP have led to renewed interest in dietary and lifestyle changes in the prevention and treatment of HDP, as well as the promotion of more restricted gestational weight gain within the 2009 Institute of Medicine recommendations.

Pre-eclampsia originates in the placenta. Various factors are released, which result in antagonism of angiogenesis, immune maladaptation, oxidative stress, and endothelial dysfunction. These, collectively, lead to the maternal syndrome that is most commonly manifest by new hypertension and proteinuria. Whether dietary change, supplementation with micronutrients, or both, may favourably influence the pathophysiological events that lead to the clinical diagnosis of pre-eclampsia and thereby prevent it, is discussed in the chapter on predicting and preventing the onset of pre-eclampsia. Here, we will discuss whether dietary changes, supplementation with micronutrients, or both, may favourably influence maternal and perinatal outcomes, once pre-eclampsia (or another HDP) has been diagnosed. Specifically, we need to consider women with pre-existing hypertension, gestational hypertension (that is isolated without evidence of pre-eclampsia), or pre-eclampsia (usually defined by proteinuria). For women with a HDP, of whatever variety, few data are available on the benefits or risks of dietary change on pregnancy outcome.

Dietary change

We were unable to identify trials examining the effect (on pre-eclampsia or other pregnancy outcomes) of ongoing salt restriction among women with pre-existing hypertension. Among women with 'gestational hypertension' (i.e. diastolic blood pressure>85 mmHg with either oedema or weight gain above 1 kg/wk), new salt restriction did not favourably influence outcomes (one trial, 361 women).[1] We were also unable to identify trials of new salt restriction among women with pre-eclampsia;

however, new salt restriction cannot be recommended on the basis of results of an observational study, which found that a low-salt diet did not decrease blood pressure but did accelerate volume depletion, a theoretical harm.[2]

For any of the HDP, we were unable to identify trials that looked at the effect on pregnancy outcome of a heart-healthy diet or calorie restriction (among women who are overweight).

Physical activity

Exercise

Outside pregnancy, increased physical activity is recommended for blood-pressure reduction. Increasingly, physical activity is recommended in pregnancy. No trials were identified that examined the effect of exercise on outcomes among pregnant women with hypertension. The PARmed-X for Pregnancy guideline for assessment of physical activity readiness in pregnancy,[3] lists pre-existing hypertension as a relative contraindication, and both gestational hypertension and pre-eclampsia as absolute contraindications to vigorous exercise.

Reduced physical activity

There has been great enthusiasm for making reduced physical activity part of the management strategy for women with a HDP, particularly pre-eclampsia. These recommendations, however, are based on tradition rather than solid evidence. The definition of bed rest, however, has varied widely, and compliance with recommendations questioned.[4]

Workload reduction or cessation are commonly recommended for outpatients with pre-existing or non-severe gestational hypertension or pre-eclampsia. However, no trial data are available to support this practice.

The effectiveness of bed rest is discussed in the section on place of care below, as relevant trials have not examined bed rest distinct from participation in an antepartum home-care programme for outpatients, or hospitalisation.

Other lifestyle changes

Outside pregnancy, stress management may be useful if stress seems to be associated with hypertension.

Place of care

Out-of-hospital care

Out-of-hospital care for women with any of the HDP, but particularly pre-eclampsia, assumes that women do not have either severe disease or severe hypertension. It also assumes that, particularly for women with gestational hypertension or pre-eclampsia, full maternal and fetal assessment has been undertaken or is planned.

The options for outpatient care include obstetric day units and antepartum home-care programmes. Eligibility criteria for outpatient care of this type vary widely, but usually describe women who live reasonably close to hospital, have blood pressure that is not particularly labile and definitely not severe, have no significant co-morbid conditions that require intensive monitoring, are likely to comply with care protocols, and can be relied upon to report a change in maternal or fetal status.

Obstetric day unit

Eligibility for care in an obstetric day unit varies from 30–60% of women assessed.[5,6] Women prefer this type of care,[5] and costs are similar despite reductions in inpatient days of care. Trials have focused on gestational hypertension, and shown similar maternal and perinatal outcomes whether women are cared for in hospital obstetric day units or as inpatients (two trials, 449 women).[6,7]

Antepartum home-care programme

Of women considered for care by a formal home-care programme, about 25% are eligible.[8] Although programmes vary in their details, all involve some component of daily contact and (usually) a weekly hospital or office outpatient visit. Some component of bed rest is also the norm.

Women can accurately measure blood pressure at home using an automated device.[9] Although those blood-pressure values are not consistently different from those measured in hospital, they vary widely, with differences ranging from 8.5 mmHg below to 15.4 mmHg above values during hospitalisation compared with non-hospitalised days, particularly among women receiving antihypertensive treatment.[10] No trials were identified that compared a formal antepartum home-care programme with either hospital day care or inpatient care. In observational studies of antepartum home care (compared with inpatient care), hospital admission (25%)[11] and re-admission rates (44%)[12] were quite high. Home care, however, was less costly while resulting in similar maternal and perinatal outcomes among women with gestational hypertension (592 women)[13] or mild pre-eclampsia (321 women).[8]

Inpatient care with or without bed rest

For women with gestational hypertension, some bed rest in hospital (compared with routine activity at home) decreased the occurrence of severe hypertension (RR 0.58, 95% CI 0.38 to 0.89) and preterm birth (RR 0.53, 95% CI 0.29 to 0.99) (two trials, 304 women).[14,15] Whether the effects were a result of bed rest or hospitalisation was not known. One of the trials enrolled 33 women with pre-existing hypertension, but results for these women were not reported separately.[14] The same trial was conducted in a health-care setting that is not applicable to that in most well-resourced settings. Women preferred unrestricted activity at home, with 49% of hospitalised women reporting that they would choose different management for a future pregnancy, compared with 16% of women allocated to routine activity at home.[14–16]

For women with pre-eclampsia, two small trials have compared strict bed rest, with some bed rest, for hospitalised women.[16,17] Among women with non-proteinuric hypertension, strict bed rest reduced the risk of severe hypertension (RR 0.58, 95% CI 0.38 to 0.89) and a borderline reduction in the rate of preterm birth (two trials, 145 women).

As risks are associated with bed rest, including thromboembolism and social and economic disruption for outpatients[3,18,19] bed rest must be shown to be beneficial before it can be recommended as part of routine inpatient (or outpatient) care (National Institute for Health and Clinical Excellence guidelines[20]). Recommendations for thromboprophylaxis associated with bed rest are available (Royal College of Obstetricians and Gynaecologists Green-top guideline 37).[21]

Antihypertensive treatment

The goals of antihypertensive treatment in pregnancy are to both optimise pregnancy outcome and avoid the complications of acute severe hypertension. The goals are not to prevent cardiovascular disease in later life. Most trials have enrolled a 'mixed' population of women with various HDPs. The blood-pressure treatment thresholds and goals are not different depending on the HDP. However, the goals are lower in the presence of pre-existing maternal co-morbidities, such as pre-gestational diabetes or renal disease, as these women are treated to lower blood-pressure goals outside pregnancy. It is generally agreed that that severe hypertension (i.e. $\geq$160–170/110 mmHg; (see Chapter on assessment, surveillance and prognosis) should be treated in pregnancy to decrease maternal morbidity and mortality.[22] Treatment of non-severe hypertension (i.e. 140–159/90–109 mmHg) is far more controversial.

Severe hypertension

Most women with severe hypertension in pregnancy will have pre-eclampsia, and the rise in their blood pressure may be acute. Given theoretical concerns about loss of cerebrovascular autoregulation in association with such potentially large and acute increases in blood pressure, the severe

hypertension of pre-eclampsia is considered to be a hypertensive 'urgency', even in the absence of maternal symptoms, such as headache. Severe elevations of blood pressure (i.e. ≥160/110 mmHg) should be confirmed, after 15 min, before antihypertensive treatment is given.

Antihypertensive drugs

As the need for treatment of severe hypertension is accepted, all relevant trials have compared one antihypertensive agent with another. Most agents have been given parenterally, with the exception of nifedipine. A few trials have also given labetalol or hydralazine orally.

Obstetricians most frequently prescribe parenteral hydralazine or labetalol for treatment of severe hypertension. A meta-analysis of the relevant trials (21 trials, 1085 women) found that, compared with other short-acting antihypertensives (including nifedipine capsules), parenteral hydralazine was associated with more adverse effects, including maternal hypotension, caesarean section, and adverse fetal-heart rate effects.[23] It must be emphasised, however, that hypotension may result with any short-acting antihypertensive agent given to women with severe hypertension, even without evidence of pre-eclampsia; these women are commonly intravascularly volume depleted. Therefore, it may be prudent to continuously monitor fetal heart rate until blood pressure has stabilised. In the same meta-analysis, labetalol was found to be associated with more neonatal bradycardia (which required intervention in one out of six affected babies)[24]; however, this does not seem to be a problem in clinical practice.

Oral labetalol has been used successfully for hypertensive urgencies as part of a general management protocol for pre-eclampsia.[25] In the 2010 NICE guidelines,[20] oral labetalol is included in the list of first-line agents for treatment of severe hypertension.

The nifedipine preparations that are appropriate for treatment of severe hypertension are the capsule and the intermediate-acting tablet,[26] although the availability of the latter is becoming restricted. Most investigators of randomised trials did not specify whether nifedipine capsules were bitten (before swallowing), which may have a greater effect on blood pressure. Use of the 5 mg (compared with 10 mg) capsule may reduce the risk of a precipitous fall in blood pressure, but no studies have compared the 5 mg and 10 mg doses.

$MgSO_4$ should not be used as an antihypertensive *per se*. When $MgSO_4$ is used for other indications (such as eclampsia prophylaxis or treatment, or for fetal neuroprotection), a loading intravenous (iv) dose of 2–5 g may be associated with a transient fall in blood pressure 30 min later,[27–30] but this has not been consistently shown.[31] The concomitant use of $MgSO_4$ and nifedipine has no contraindication, as the risk of neuromuscular blockade is less than 1%,[32] and blockade is reversed with 10 g of intravenous calcium gluconate.

Nitroglycerine is primarily venodilatory. Theoretically, it may not be a good choice of antihypertensive drug in women with pre-eclampsia. However, no adverse clinical effects have been shown in small studies.[33,34] Diazoxide was previously associated with excessive maternal hypotension, but more recently, low-dose diazoxide (15 mg iv) resulted in similar outcomes compared with hydralazine (5 mg iv) in one small trial.[35] For refractory hypertension, in an intensive-care setting, use of sodium nitroprusside can be considered. In a case series of 22 women (24 fetuses), the stillbirth rate was 27.8%, but the investigators attributed these deaths to the underlying disease process, rather than to the nitroprusside.[36]

For non-severe hypertension

How to manage non-severe blood pressure (140–159/90–109 mmHg) is controversial. Any antihypertensive treatment will, compared with placebo or no treatment, decrease the risk of transient, severe hypertension (RR 0.50, 95% CI 0.41 to 0.61; 19 trials, 2409 women; NNT 9 to 17), without a clear difference in other maternal or perinatal outcomes, such as stroke, pre-eclampsia, perinatal death, or preterm delivery (28 trials, 3200 women).[37] Antihypertensive treatment, however, may actually be harmful, on the basis ofresults of a small pilot randomised-controlled trial and a meta-regression of randomised-controlled trials, which found a significant relationship between the antihypertensive-induced fall in mean arterial pressure and the risk of small gestational age infants or infants with lower birthweight.[37–40]

Otherwise healthy women

For women without co-morbid conditions, a wide range of acceptable blood-pressure thresholds is available that is consistent with the published evidence: 140–159/90–105 mmHg. Choosing an upper-limit treatment blood pressure threshold of 159/105 mmHg acknowledges intra-patient variability in blood pressure, the inaccuracies of blood-pressure measurement, the desire to avoid severe hypertension (severe blood pressure $\geq$160–170 mmHg or diastolic blood pressure $\geq$110 mmHg), and the recognition that outside of pregnancy, non-severe hypertension is not an indication for immediate treatment. Therefore, a reasonable target blood pressure of antihypertensive treatment is 130–155 mmHg systolic, and 80–105 mmHg diastolic.

Women with co-morbid conditions

For women with co-morbid conditions, blood pressure should be normalised, with a reasonable goal being 130–139/80–90 mmHg. Choosing a higher blood-pressure goal than the non-pregnancy recommendation of blood pressure less than 130/80 mmHg represents a compromise between maternal protection and maintenance of placental perfusion.

Although some treatment guidelines have chosen lower blood-pressure treatment goals for women with pre-eclampsia, antihypertensive treatment does not decrease maternal morbidity in pre-eclampsia or eclampsia.[37] However, in some circumstances (e.g. severe headache) it seems prudent to normalise blood pressure, and others in which it may not (e.g. absent end-diastolic flow in the fetal umbilical artery).

Antihypertensive drugs

When a decision is made to use antihypertensive treatment, no definitive data are available to guide the choice of agent. Treatment is most commonly required in the third trimester of pregnancy when blood pressure is on the rise, such that an increase in antihypertensive dose should be anticipated. Guidance for use of specific antihypertensive medications does not differ by the type of HDP.

The relevant antihypertensive agent compared wit placebo (or no therapy) trials have been designed to determine the relative benefits and risks of treatment, as discussed above. The following agents have been compared with placebo or no treatment (with treatment when blood pressure has reached a diastolic of 100–110 mmHg): methyldopa, labetalol (a combined alpha and non-selective beta-blocker), beta-blockers (acebutolol, mepindolol, metoprolol, pindolol, and propranolol), calcium channel blockers (isradipine, nicardipine, nifedipine, and verapamil), hydralazine, prazosin, and ketanserin (28 trials, 3200 women).[37]

In comparative trials of one antihypertensive drug compared with another for non-severe hypertension, most commonly, beta-blockers have been compared with methyldopa. Beta-blockers (i.e. labetalol, pindolol, metoprolol or oxprenolol) may be more effective antihypertensive drugs than methyldopa (RR 0.75, 95% 0.58 to 0.94) (10 trials, 539 women), but no other differences in maternal or perinatal outcomes have been shown (19 trials, 1282 women).[37,41]

In international clinical practice, labetaolol and methyldopa are the most commonly used agents for non-severe hypertension in pregnancy. No reliable data are available on long-term developmental outcomes to guide one's choice of antihypertensive agent. Limited data from placebo-controlled trials have not revealed adverse effects of (any) antihypertensive agent on health or neurodevelopment assessed at 1 year (nifedipine, 110 children),[42] 18 months (atenolol, 190 children),[43] or 7.5 years (methyldopa, 242 children)[44] in placebo-controlled trials. Emerging observational data on the neuro-developmental effect of methylopa and labetalol have raised concerns about each. Methyldopa treatment and duration (25 children) was associated with a negative effect on children's performance IQ at 4–5 years of age, compared with labetalol (32 children).[45] On the other hand, labetalol, compared with methyldopa, was associated with a heightened risk of attention deficit hyperactivity disorder in children of primary school age (202 children).[46] This highlights the need to first determine whether antihypertensive treatment for non-severe hypertension in pregnancy is necessary.

Mention should be made of a few specific agents that should not be used in pregnancy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are fetotoxic, especially to the fetal kidney. The bulk of the evidence also suggests that these agents are teratogenic (see section on aspects of care specific to women with pre-existing hypertension, below). As with other drugs used

commonly to treat the HDP, a number of ACE inhibitors are, however, acceptable for use during breastfeeding.[20,47]

Thiazide diuretics can be considered for use. Concerns that they may inhibit the normal plasma volume expansion of pregnancy did not translate into a heightened risk of pre-eclampsia, or any difference in adverse maternal or perinatal outcomes (five trials, 1836 women).[48] It is not clear why atenolol (compared with other cardioselective beta-blockers) may be associated with adverse effects on fetal growth[49]; however, until new data are available, it may be prudent to use other agents. More stillbirths were reported in the prazosin arm of one trial.[50] Oral hydralazine is associated with more maternal side effects if used as monotherapy.[51]

Oral antihypertensive drugs do not seem to change fetal heart rate or pattern, but the data are not robust[52]; a cautious approach would be to not attribute changes in fetal heart rate or pattern to an antihypertensive distinct from its haemadynamic effects.

Aspects of care specific to women with pre-existing hypertension

Many women of child-bearing age are hypertensive, and the increasing rate of obesity and advanced maternal age are associated with increased rates of pre-existing hypertension in pregnant women. The issues to consider are presented in Table 1.

Pregnancy is associated with a physiological fall in blood pressure, which reaches its nadir at about 20 weeks' gestation. This early pregnancy fall in blood pressure can obscure pre-existing hypertension but also may allow for the withdrawal of antihypertensive treatment, at least until late in the second trimester when blood pressure is rising again towards pre-pregnancy levels by term. Of course, any rise in blood pressure in the second half of pregnancy must always be distinguished from the superimposed gestational hypertension of pre-eclampsia.

Women with pre-existing hypertension have an increased risk of accelerated hypertension in the third trimester and superimposed pre-eclampsia (20%), and also a heightened risk of fetal growth restriction, placental abruption, preterm delivery and stillbirth. These events are neither restricted to women with superimposed pre-eclampsia, nor related to actual blood-pressure levels.

Woman with pre-existing hypertension, whether essential or secondary to a co-morbid condition (i.e. renal disease), should be observed frequently during pregnancy by maternity care providers familiar with the management of the HDP. Heightened surveillance as part of outpatient or inpatient care is recommended for women with worsening hypertension, proteinuria, or both, at any stage of pregnancy. This facilitates assessment of maternal and fetal well-being and inter-disciplinary

Table 1
Pre-pregnancy planning for women with pre-existing hypertension.

Before pregnancy	In pregnancy	Postpartum
Investigate for underlying conditions as applicable (e.g. endocrine, renal, vascular)	Consider ceasing antihypertensive therapy if the woman demonstrates a physiological fall in blood pressure	Recommence usual antihypertensive treatment as long as it is compatible with breastfeeding
Assess for end-organ damage	Monitor for signs of superimposed pre-clampsia after 20 weeks' gestation	Optimise lifestyle, diet and weight
Change to an antihypertensive drug that is acceptable for use in pregnancy	Assess for proteinuria at every visit	
Optimise lifestyle, diet and weight	Laboratory assessment if worsening hypertension or proteinuria	
	Assess fetal growth and well-being if indicated	
	Identify a clear blood pressure treatment target for each woman	

discussion. The reader is referred to other sources for information about the investigation and management of secondary causes of hypertension.[53]

Teratogenicity of antihypertensive medication

Inadvertent first-trimester exposure to antihypertensive agents should be anticipated to occur in about half of women with pre-existing hypertension, as this proportion of pregnancies are unplanned. As such, considerations in these women include the potential for teratogenicity of antihypertensive drugs used and also the adequacy of contraception.

The potential teratogenicity of antihypertensive drugs must be considered in relation to the baseline risk of major malformations: 1–5% of pregnancies. None of the antihypertensive agents used commonly in pregnancy are known to be teratogenic, but the quality of the information is only fair for most agents.[54]

The use of ACE inhibitors and ARB is contraindicated in pregnancy; after first-trimester exposure, these drugs have been associated with an increased risk of fetal, particularly cardiovascular, malformations, in addition to their fetotoxic effects after exposure later in pregnancy.[55,56] Diuretics such as hydrochlorothiazide, although not teratogenic, may restrict the natural plasma volume expansion of pregnancy and are not recommended for the treatment of hypertension. All of the agents used in pregnancy, as well as some ACE inhibitors, are compatible with breastfeeding on the basis of findings of low drug levels in breast milk. This makes it unlikely that the neonate would ingest enough to have a pharmacological effect.[47] The potential for atenolol to reduce fetal growth velocity has been reported, particularly with use from early pregnancy, although data are not definitive.[57]

When ACE inhibitors or ARB have been given for renoprotection before pregnancy, one must bear in mind that no alternative agent for this purpose is acceptable for use in pregnancy. Also, it is normal to take up to 12 months to conceive and, as such, women may be without renoprotection for a prolonged period before conception.

Thromboprophylaxis

Pre-eclampsia (but not the other HDP) increases thromboembolic risk by a factor of three.[58] In addition, many of both the risk markers for pre-eclampsia (i.e. age older than 35 years, obesity, multiple pregnancy, or renal disease with nephrotic syndrome) and aspects of pre-eclampsia management (i.e. bed rest or caesarean section) put these women at further thromboembolic risk. Although it is not clear how much risk is increased with multiple risk factors, both the relevant 2008 CHEST guidelines[58] as well as the 2007 Royal College of Obstetricians and Gynaecologists) guidelines[21] recommend individualised risk assessment for determination of thromboprophylaxis need. As pre-eclampsia is considered to be an antenatal and postnatal risk factor for thrombosis, antenatal thromboprophylaxis is recommended for these women in the presence of two additional antenatal risk factors (i.e. hospitalisation and obesity) or one additional postnatal risk factor (i.e. elective caesarean section or systemic infection). The reader is referred to the individual guidelines for further information about anticoagulant choice, dosing and duration of treatment.

Aspects of care related to anaesthesia and fluid management

The importance of early anaesthetic involvement in the care of women with a HDP, particularly pre-eclampsia, was highlighted in the 2007 Confidential Enquiry into Maternal and Child Health report.[22] Important contributors to these deaths were inadequate pre-operative control of systolic blood pressure and failure to prevent the hypertensive response to intubation.

Early anaesthetic consultation can provide advice about blood-pressure control (including early epidural analgesia to obtund the sympathetic response to pain), timing of labour analgesia (before coagulation becomes abnormal), and the potential hazards of general anaesthesia (possible difficult airway and hypertensive response to intubation). The anaesthetist can also insert an arterial line for both continuous blood-pressure monitoring and serial blood sampling.

Coagulation and drugs affecting coagulation

In parturients with pre-eclampsia, the platelet count can fall precipitously. The anaesthetist uses the absolute platelet count, trend in platelet number, past history of bleeding, and evidence of any current bleeding to determine the optimum technique for analgesia and anaesthesia in order to avoid serious bleeding.

A primary concern is that insertion of a needle into the epidural or subarachnoid space with a coagulation abnormality may cause bleeding into that space (i.e. neuraxial haematoma) and catastrophic neurological impairment. Neuraxial haematomas are rare, occurring in about one in 200,000 deliveries, either spontaneously, or in association with altered coagulation. No ideal test is available to determine the risk of this event. Bleeding into the epidural space has not been associated with platelet counts above 75×10^9/L.[59] Thromboelastography studies in women with pre-eclampsia confirm that when the platelet count is greater than 75×10^9/L, coagulation is normal.[60,61] However, as abnormal results on thromboelastography (or other tests of platelet function) do not always correlate with an increased incidence of bleeding,[62] tests of platelet function are not part of routine clinical care. Given the uncertainties, some anaesthetists are reluctant to insert a neuraxial block in even healthy women when the platelet count is not at least 100×10^9/L.[63]

Use of low-dose aspirin is not a contraindication to neuraxial block, and it may be continued right up until delivery.[64] In women on low molecular weight heparin, the European Society of Regional Anaesthesia and American Society of Regional Anesthesia recommend delaying neuraxial block for up to 10–12 h after a prophylactic dose and at least 24 h after a therapeutic dose.[65] Some anaesthetists wait longer as the true risk after any dose of low molecular weight heparin is unknown, particularly if the parturient is on other medications that affect coagulation. As unfractionated heparin has a shorter half-life, some clinicians switch to unfractionated heparin at 34–36 weeks, to increase the chance that neuraxial block will be an option to control labour pain or for anaesthesia for caesarean delivery.

Epidural and other forms of analgesia

In woman with pre-eclampsia, an early epidural is highly recommended for a number of reasons. First, effective analgesia during labour can ablate the pain-induced sympathetically mediated increase in blood pressure, an effect that can be exaggerated in women with pre-eclampsia.[66,67] Second, early insertion of an epidural may avoid the subsequent dilemma of whether or not it is safe to undertake neuraxial block when the platelet count is still greater than $75–100 \times 10^9$/L but is falling. Finally, if maternal or fetal compromise occurs and delivery is necessary, time allowing, the epidural may be topped up to provide anaesthesia for instrumental or operative delivery, minimising the risks associated with general anaesthesia.

Epidural analgesia has not been shown to harm the fetus or increase operative delivery risk in women with severe pre-eclampsia.[68] In women with a contraindication to epidural analgesia, pain relief can be provided by short-acting intravenous opioids (i.e. fentanyl or remifentanil).[69] These (and particularly remifentanil) are associated with a heightened risk of maternal and neonatal respiratory depression. Maternal monitoring should include respiratory rate and pulse oximetry, even when the opioids are given using a patient-controlled device.[70] A paediatrician should be in attendance at delivery in the event that neonatal resuscitation is required.[71]

Anaesthesia for operative delivery

All of the following are acceptable methods of anaesthesia for operative delivery of a women with a HDP: epidural, spinal, combined spinal-epidural, or general anaesthesia.

Neuraxial anaesthesia (compared with general anaesthesia) is both preferable and more widely used. Difficult or failed intubation is more common among parturients, possibly due to either oedema affecting the laryngeal inlet in pre-eclampsia,[72,73] or to a lack of experience with intubation in pregnancy, or both, among those practitioners who spend most of their time on obstetric wards. In addition, there is also the potential for intubation to significantly increase blood pressure, as previously

discussed.[22,74] If neuraxial anaesthesia is inadequate or rapid delivery of the fetus is necessary, general anaesthesia may be carried out, and the hypertensive response to intubation blunted by short-acting opioids (fentanyl, alfentanil, remifentanil), antihypertensive agents (e.g. nifedipine, labetatolol, or nitroglycerin), local anaesthetics, or all.[75–78]

Within neuraxial anaesthesia, there are advantages and disadvantages of epidural compared with spinal anaesthesia. Epidural anaesthesia has a slower onset, potentially lowering the risk of hypotension. The epidural catheter can be used to provide postoperative analgesia and aid in pain-induced blood-pressure control. On the other hand, spinal anaesthesia has a more rapid onset, and the smaller needle should, theoretically, lower the risk of trauma to neuraxial blood vessels and neuraxial haematoma. As with epidural anaesthesia, spinal anaesthesia has not been associated with detrimental effects on maternal blood pressure or uteroplacental blood flow.[79]

If a woman with severe pre-eclampsia requires urgent (caesarean) delivery and shows signs of severe neurological dysfunction (e.g. increased intracranial pressure, Glasgow coma score less than 8), the principles of neuroanaesthesia should be followed. These principles include airway protection through endotracheal intubation, maintenance of normocapnia (i.e. a pCO_2 of 30–32 mmHg, which is normal for pregnancy), obtundation of the pressor response to intubation, and maintenance of haemodynamic stability (i.e. stable blood pressure) to preserve cerebral perfusion.

Fluid management

Pulmonary oedema has been a leading cause of mortality in pre-eclampsia.[22] Fluid balance should be carefully monitored. Oliguria may be tolerated for several hours, particularly after surgery when antidiuretic hormone levels are high, and should not be treated aggressively with fluid boluses or furosemide. Studies evaluating the benefits of furosemide or dopamine have not shown a benefit in the treatment of persistent oliguria in pre-eclampsia.[80,81]

Sympathetic blockade after neuraxial analgesia, anaesthesia, or both, can cause profound hypotension in the healthy parturient. Unfortunately, this profound hypotension cannot be prevented by the common practice of giving a pre-load of 500–1000 ml of normal saline.[82] Given the propensity of women with pre-eclampsia to go into pulmonary oedema, pre-loading should not be practised unless there is some other indication, such as fetal heart rate abnormalities. How to optimally treat hypotension resulting from sympathetic blockade is unclear. Both ephedrine and phenylephrine have been used for spinal-induced hypotension in women with pre-eclampsia,[83] but the optimal dose and timing are not known. As the response to any vasopressor is likely to be exaggerated in pre-eclampsia, one should use a small dose and monitor the effect closely.

Invasive monitoring

Most women with a HDP may be effectively monitored by vital signs and pulse oximetry. The use of a Modified Early Obstetric Warning System chart may provide timely recognition of deterioration in maternal status and expedite treatment, although this approach requires validation.[22] Insertion of an arterial line will allow for both titration of intravenous antihypertensive agents and serial blood sampling, particularly in the face of laboratory abnormalities.

No correlation exists between pulmonary capillary wedge pressure and central venous pressure measurements in pregnancy. As such, absolute values should not be used to diagnose the status of intravascular volume or left-sided cardiac pressures. Only trends in central venous pressure measurements may be useful; for example, in monitoring the response to fluid administration in the setting of significant obstetric haemorrhage. In rare cases, when a pulmonary artery catheter is deemed necessary to monitor a woman's haemodynamic status, it should be inserted by experienced personnel.

Minimally invasive or non-invasive haemodynamic monitors are currently being studied in women with pre-eclampsia. Preliminary data indicate that haemodynamic changes in these women can be profound. Langesaeter[84] documented profound changes of increased systemic vascular resistance and heart rate, and decreased cardiac output in a woman with pre-eclampsia during the second stage of labour, even though the woman felt no pain.

Practice points

- Bed rest cannot be recommended for women with any of the HDP until the benefits can be shown to outweigh the thromboembolic risks.
- Many women with HDP are at increased thromboembolic risk, and clinicians should be aware of detailed guidelines for risk assessment.[21,58]
- Antihypertensive treatment is strongly advised for women with severe hypertension (i.e. $\geq$160/110 mmHg). The most common agents used are parenteral labetalol or hydralazine, or oral nifedipine capsules.
- No consensus exists on when antihypertensive therapy is required for non-severe hypertension (i.e. 140–159/110 mmHg), because the relative maternal benefits (decreased severe hypertension) and fetal risks (poorer fetal growth) are not understood. A woman's blood-pressure goal should be made explicit. Labetalol and methyldopa are the agents used most commonly.
- Breastfeeding is acceptable with most antihypertensive agents, including some ACE inhibitors.
- Fifty per cent of pregnancies are unplanned so women with pre-existing hypertension may inadvertently conceive on antihypertensive treatment.
- ACE inhibitors and ARBs are contraindicated for use in pregnancy as they are fetotoxic and probably also teratogenic.
- Anaesthetists play a critical role in the management of women with a HDP, and should be involved earlier rather than later in the course of their care.
- Low-dose aspirin is not a contraindication to neuraxial anaesthesia.
- No ideal method is available to determine the risk of neuraxial haematoma associated with neuraxial anaesthesia, but this complication is rare (i.e. 1/200,000 deliveries). Bleeding into the epidural space has not been associated with platelet counts above 75×10^9/L.
- Hypotension that may result from neuraxial analgesia, anaesthesia, or both, cannot be prevented by the common practice of giving a pre-load of normal saline, and this practice has the potential to increase the risk of pulmonary oedema.

Research agenda

- Few data are available to guide use of non-pharmacological approaches to HDP. Research is urgently needed into the relative benefits and risks of bed rest, particularly for women on antepartum home care, as women in hospital are primarily resting in bed anyway.
- For the management of severe hypertension, clinicians should familiarise themselves with multiple agents, and future research should evaluate a broader range of approaches, including other oral monotherapy or dual drug therapy, as recommended outside pregnancy.
- The priority of research into treatment of non-severe hypertension should be the determination of whether antihypertensive therapy is needed to optimise perinatal and maternal outcome; if so, research can further explore whether one agent is superior to another.
- Pulmonary embolism is a leading cause of maternal death in well-resourced settings; as women with the HDP often have multiple thromboembolic risk factors, research is needed to validate thromboprophylaxis guidelines.
- Obstetric care would also benefit greatly from reliable non-invasive techniques for measuring fluid status in pre-eclampsia.

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