

Therapeutic strategies for the prevention and treatment of pre-eclampsia and fetal growth restriction

Charlotte Oyston

Philip N Baker

Abstract

Fetal growth restriction and pre-eclampsia are common pregnancy complications that contribute significantly to maternal and perinatal morbidity and mortality, and long term health outcomes. The underlying aetiology of these conditions is placental under-perfusion and ischemia. Most prophylactic and treatment measures for these conditions are hypothesized to have effect through improved placental perfusion, or reduced oxidative stress, inflammation and subsequent placental damage. However, while many therapies have biologic plausibility, there is a lack of high quality evidence that they substantially improve important outcomes such as birth weight, prematurity, mortality or serious morbidity. This review will describe therapies currently available in clinical practice for the prevention and treatment of pre-eclampsia and intrauterine growth restriction, and outline some promising new therapies, which may change the way these conditions are managed in the future.

Keywords fetal growth restriction; pre-eclampsia; pregnancy complications; pregnancy outcome; prevention

Introduction

Pre-eclampsia (PE) and severe or early onset fetal growth restriction (FGR) account for a substantial proportion of preterm deliveries, maternal and perinatal morbidity and mortality. While they are distinct conditions, they may occur together, and are often considered together as they share a common aetiology of inadequate placental perfusion. In normal pregnancy, the terminal vessels of the maternal uterine circulation (the spiral arteries) undergo an ordered progression of changes from the first trimester. Extra-villous trophoblasts migrate from the placenta and invade and replace the endothelium and muscular walls of the spiral arteries supplying the placental bed. Modified spiral

arteries lose their muscular wall, the vessel lumen becomes distended, and the vessels become flaccid, funnel shaped and void of vasoconstrictor ability. Functionally, this allows large volumes of maternal blood to pool in the intervillous space where it surrounds the fetal vessels, allowing transfer of oxygen and nutrients to occur between mother and fetus. The vascular adaption of the spiral arteries is thought to be complete by mid to late second trimester. If these changes are inadequate, placental perfusion may become compromised and result in placental ischemia. Oxidative stress and inflammation result, and may further damage the placenta, resulting in FGR, or trigger release of factors into the maternal circulation which cause endothelial dysfunction and the resultant clinical syndrome of PE.

This article reviews the therapies currently in use for the prevention and treatment of PE and FGR, as well as potential new therapies currently under development. Aspects concerning screening, diagnosis, antenatal surveillance and timing of delivery are beyond the scope of this review and will not be discussed.

Case 1. fetal growth restriction – therapies for prevention

Miss FB is a healthy 28 year old G2P1. Her previous pregnancy was complicated by severe growth restriction and she delivered a 2.1 kg baby at 36 weeks' gestation. The placenta from this pregnancy was small with multiple infarcts and features of maternal vasculopathy at histology. FB comes to see you at ten weeks gestation in her next pregnancy, requesting advice on minimising her risk of FGR in this pregnancy.

What prophylactic treatments will reduce FB's risk of this pregnancy being complicated by FGR?

Aspirin

Aspirin is the most studied prophylaxis for the prevention of FGR and PE. Aspirin inhibits the production of prostacyclin (a vasodilator) and thromboxane (a vasoconstrictor), both of which are present in the utero-placental circulation. When given at low doses, aspirin selectively inhibits production of thromboxane, but not prostacyclin. It is thought that antenatal low dose aspirin therapy could result in less vasoconstriction and reduce thrombosis of the vessels within or supplying the placenta, thereby improving blood flow and protecting against FGR and PE. More recently, other mechanisms have been identified through which low dose aspirin may protect against FGR; these include increasing production of vasodilator nitric oxide, and reducing injury due to oxidative stress and inflammation through the heme-oxygenase-1 pathway.

Large systematic reviews suggest that aspirin reduces the risks of FGR, preterm delivery, and preterm PE (see below section for further discussion). A meta-analysis including over 37,000 women found that use of aspirin significantly reduced the number of infants born with a birth weight below the 10th centile, preterm delivery and PE (relative risk reduction of 10%, 8% and 17% respectively). Similarly, the Perinatal Antiplatelet Review of International Studies (PARIS) – an analysis of individual data from over 32,000 women - concluded that antiplatelet agents reduced preterm delivery and PE by 10%, although there was no difference in the number of infants born with a birth weight below the 10th centile.

Charlotte Oyston BMedSci(Hons) MB ChB PGDipOMG PhD, FRANZCOG is an Obstetrician at Middlemore Hospital, Auckland, New Zealand, and a Senior Lecturer in Obstetrics and Gynaecology at the University of Auckland, Auckland, New Zealand. Conflicts of interest: none declared.

Philip N Baker BMedSci BM BS DM FRCOG, FMedSci The College of Life Sciences, University of Leicester, Leicester, UK. Conflicts of interest: none declared.

Smaller meta-analyses designed to look for benefits amongst subgroups of women suggest that the reduction in perinatal death, FGR and preterm birth is limited to those who commence aspirin therapy before 16 weeks' gestation. The concept of a critical window for initiating prophylaxis is biologically plausible. If prophylaxis is to be effective then it may need to be commenced before trophoblast invasion is complete. Deep invasion of the trophoblast invasion is evident by 16 weeks' gestation and thought to be complete by the late second trimester. Therefore, starting aspirin prior to 16 weeks' gestation may influence the adaption of the deeper myometrial spiral arteries. The results from these subgroup analyses must be interpreted with caution, as they do not include all published data from pregnancies where aspirin was commenced before 16 weeks', as in some studies recruitment overlapped 16 weeks' gestation. Furthermore, studies where aspirin was commenced prior to 16 weeks' gestation had lower numbers of participants (mean of 101 women) compared to those recruiting after 16 weeks (mean of 954 women), and meta-analyses of many small trials may be influenced by publication bias - where small trials with statistically significant findings are more likely to be published than those showing no effect.

In summary, antenatal aspirin therapy for women who are deemed to be at increased risk of PE or FGR may confer a small reduction in risk of FGR of around 10%, and there also appears to be benefits in terms of reduced risk of PE and preterm birth. The dose recommended by most national and international guidelines is 100–150 mg, and due to beneficial effect on blood pressure, it should be taken at night (see below section on pre-eclampsia). There may be certain groups in whom benefit is more pronounced - for example women who start aspirin prior to 16 weeks' gestation, however further study is required before conclusive recommendations can be made in regards to additional benefits in subgroups of women.

Therapies which do not prevent FGR

Anti-coagulants

Both PE and FGR are associated with placental thrombosis and ischaemia. This association has prompted the study of anti-coagulation as prophylaxis for these conditions, particularly in women with a thrombophilia. Heparin and low molecular weight heparins (LMWH) are the anticoagulants of choice in pregnancy as they have a favourable safety profile, and do not cross the placenta. Heparins also have anti-inflammatory, immune modulating and angiogenesis promoting properties, and it has been hypothesized that these properties may result in improved pregnancy outcomes for women at high risk of PE or FGR.

Women with an acquired thrombophilia: antiphospholipid syndrome (APS) is an autoimmune disorder characterized by a history of vascular thrombosis or pregnancy morbidity (including early onset FGR, PE and placental abruption) and the presence of antiphospholipid antibodies. Antenatal heparin is recommended for thrombo-prophylaxis in women with a history of thrombus, and women with a history of recurrent pregnancy loss have an increased live birth rate following combination treatment with unfractionated heparin and aspirin. However there is a lack evidence for the use of heparin solely for the

prevention of FGR and PE in women with APS, and unfortunately, further clinical trials to clarify this matter seem unlikely. A multicentre study of the use of heparin for prevention of PE was abandoned after only recruiting 32 women in 9 years, with the pre-existing widespread use of antenatal heparin possibly contributing to low recruitment.

Women with and without inherited thrombophilias: inherited thrombophilias include conditions such as factor V Leiden, prothrombin gene mutation, and deficiencies of anti-thrombin III, protein C or protein S. In contrast to APS, these conditions do not substantially increase the risk of PE or FGR. An international collaborative meta-analysis using individual patient data sourced from eight randomized controlled trials, included data from 963 women, 403 whom had an inherited thrombophilia. LMWH did not reduce the risk of recurrent placenta-mediated conditions (such as FGR or PE) in at risk pregnancies. Two further randomized clinical trials published following the IPD analysis also found no reduction in rates of FGR or PE in women treated with LMWH. In the IPD analysis, LMWH use in women with a history of placental abruption reduced placental complications in subsequent pregnancy. However, given the heterogeneity amongst study populations, and small size of the subgroup of women with a history of abruption, further research is required before LMWH can be recommended for women with a previous history of abruption. Use of LMWH or heparin for prophylaxis against PE or FGR should be reserved for well-designed randomized controlled trials evaluating their efficacy in preventing placently mediated outcomes.

Calcium

Meta-analyses have shown that use of calcium supplementation in pregnancy confers a modest but consistent reduction in risk of gestational hypertension or PE (see below) but these benefits do not appear to extend to the prevention of FGR, low birth weight or perinatal mortality.

Case 2. pre-eclampsia - therapies for prevention

Mrs PB is a 24 year old G2P1. Her previous pregnancy was complicated by severe PE necessitating delivery at 34 weeks' gestation. She has no other medical history and has a BP of 110/60 at her 12/40 booking visit. What prophylaxis can you offer PB which will reduce the risk of her developing PE in this pregnancy?

Calcium

Epidemiologic studies have demonstrated an inverse relationship between dietary calcium intake and hypertensive disorders of pregnancy. The precise mechanisms linking low calcium intake with hypertensive disorders in pregnancy are unclear. One possible explanation is that low calcium levels may increase renin and parathyroid hormone release, leading to increased intracellular calcium in vascular smooth muscle, stimulating vasoconstriction.

A Cochrane systematic review of placebo controlled trials found that calcium supplementation of at least 1 g per day in pregnancy reduces the risks of both hypertension and PE (relative risks 0.65, 0.45 respectively), although this benefit may be

limited to women at high risk of PE, or who have low dietary intake of calcium. In this meta-analysis, a reduction in risk of preterm delivery was also observed with calcium supplementation, and this was greatest for women at a high risk of PE (relative risk 0.45). Calcium supplementation also reduced a composite of maternal mortality and serious morbidity by 20%. The benefits of calcium intake did not extend to neonatal outcomes such as FGR, low birth weight or perinatal mortality. Surprisingly, calcium supplementation was associated with increased risk of HELLP syndrome (relative risk 2.67). As composite maternal mortality and serious morbidity is reduced with calcium supplementation, and HELLP is a rare complication, it is likely the overall benefits of supplementation outweigh the small absolute risk of HELLP syndrome, but it is important that any future studies looking at the effect of calcium supplementation alone or in combination with other therapies examine the incidence of HELLP syndrome.

Aspirin

There are many clinical trials evaluating the efficacy of aspirin for the prevention of PE. The conclusions drawn from these studies are often conflicting, which is unsurprising given the varying dose, gestation at commencing therapy, and baseline risk of PE in study participants. The most recent large randomized controlled trial for aspirin in the prevention of PE is the aspirin for evidenced based preeclampsia prevention (ASPREE) trial. ASPREE was a double blinded, placebo controlled trial of 150 mg aspirin nocte vs placebo taken from 11 to 36 weeks' gestation. The study included 1776 women with a singleton pregnancy who were at high risk of preterm PE based on the first trimester screening algorithm that included clinical, biochemical and biophysical measurements in risk assessment. In this study, women receiving aspirin had a 60% reduction in risk of developing PE prior to 37 weeks' (1.6 vs 4.3%), but no reduction in risk of developing PE at term. These findings are supported by the most recent meta-analyses of aspirin in pregnancy for PE prophylaxis (which includes analysis of ASPREE as well as several other recent trials), which reports a 70% reduction in risk of preterm PE if aspirin is started prior to 16 weeks' gestation, at a dose of at least 100 mg. Whilst older meta-analyses had suggested a smaller (10%) reduction in both preterm delivery and PE that occurred irrespective of gestation of initiation, in those analyses there was no division of term and preterm PE, and the dose of aspirin was low (<75 mg) in many of the studies where aspirin was commenced prior to 16 weeks', which may have masked the benefits of commencing aspirin early.

Small randomized trials suggest that aspirin may be associated with beneficial effects on blood pressure with evening, but not morning administration, in both pregnant and non-pregnant populations. This circadian effect may be due to a reduction in plasma renin activity, and altered urinary excretion of cortisol, dopamine and catecholamines which have been observed with evening, but not morning administration of aspirin. Therefore, for the prophylaxis of PE and FGR, it is prudent to prescribe aspirin to be taken at night.

Therapies that do not prevent PE

There is inadequate evidence that therapies such as exercise, reduction of dietary salt intake, diuretics or progesterone reduce

the risk of PE. While the admission of women with PE to hospital permits close monitoring of an unpredictable condition, and allows timely intervention if deterioration occurs, there is insufficient evidence to suggest that rest prevents or alters the course of the disease. As discussed above, evidence supporting the use of antenatal heparin for the prevention of PE in women with and without antiphospholipid syndrome is lacking.

Antihypertensive therapy for the prevention of PE

End-organ damage may occur as the result of severe, untreated hypertension, resulting in stroke, renal impairment or placental abruption. However, antihypertensive therapy does not prevent the evolution of chronic or gestational hypertension into PE or improve FGR. A large meta-analysis of randomized trials evaluating antihypertensive treatment for mild to moderate hypertension in pregnancy found no reduction in risk of PE, fetal death or small for gestational age (SGA) infants after treatment with any antihypertensive medication, and no clear difference in between anti-hypertensives in reducing the risk of PE.

Although antihypertensive therapy in chronic or gestational hypertension cannot prevent PE, once hypertension is diagnosed, there is evidence that tighter control of maternal blood pressure can result in improved outcomes. The Control of Hypertension in Pregnancy Study (CHIPS) randomized 987 women with chronic or gestational hypertension to tight control of BP (diastolic target 85 mmHg) or less tight (target diastolic 100 mmHg) control. This study suggests that more tightly controlled BP results in improved maternal outcomes (less cases of severe hypertension BP >160/110, less women with low platelets, and less women with elevated liver enzymes compared to less tight control). However here was no difference in serious maternal complications or those with birthweight below the 10th centile.

Antioxidant vitamins (vitamins C, E): free radicals are highly reactive molecules which are produced during oxidation reactions and initiate a chain of reactions which may cause cell damage. Antioxidants are substances which slow or stop these chain reactions by removing free radical intermediates or inhibit reactions by being oxidized themselves. In PE there is a reduction in antioxidants and an increase in oxidative stress in both maternal plasma and the placenta, possibly contributing to the widespread endothelial dysfunction resulting in the signs and symptoms of PE. Therefore, antioxidant supplements may reduce oxidative stress, and limit the systemic endothelial damage seen in PE. Antioxidant vitamins (for example, Vitamins C, E) are especially attractive as a prophylaxis against preeclampsia as they are readily available and inexpensive to produce. A large systematic review compared antioxidant use with placebo or other interventions. Just over half of the women in this review were at moderate/low risk of PE, and treatment involved vitamins C and E either alone or in combination in the majority of studies. Supplementation with antioxidant vitamins did not reduce the risk of PE, severe PE, or delivery of small for gestational age infants, compared to control. Furthermore, women taking antioxidants were *more* likely to require anti-hypertensive treatment, or report abdominal pain in late pregnancy. Late treatment initiation may have contributed to the negative findings in these studies; only two trials specifically recruited women between 12 and 20 weeks' gestation, and none of the remaining

trials analysed outcomes using the gestation at which treatment was initiated as a co-variant. When considering prophylaxis against PE, initiating treatment in the late second trimester may be too late, as the critical vascular adaptations which are aberrant in PE may already be present.

Fetal growth restriction and pre-eclampsia: what are potential new therapies for prevention and cure?

Aspirin, or aspirin and calcium, offer at best a modest reduction in risk of FGR and PE in women at risk of these conditions. There is a desperate need to develop more effective preventative strategies for these conditions. Furthermore, there are currently *no* therapies in routine clinical use which are proven to improve fetal growth or reverse the course of PE once a diagnosis is made, although antenatal corticosteroids for fetal pulmonary maturation, or Magnesium Sulphate for neuroprotection can improve neonatal outcomes related to early delivery. The following section summarises several new therapies in development for the prevention and/or treatment of FGR and PE, some of which are being trialled clinically, but none of which can be currently recommended for use outside of a research setting. These new treatments can be broadly classified as those which improve uteroplacental blood flow, or in the case of PE – reduce oxidative stress and inflammation, or those that ameliorate endothelial dysfunction, although it is likely that many of these new treatments will act in more than one way.

Nitric oxide based therapies

Nitric oxide (NO) is an important vasodilator in the placental circulation, and also plays an important role in placental development, including placental implantation and trophoblast invasion. In animal studies, inhibition of NO production in pregnancy results in structural (shorter and narrower) and functional impairments in uterine artery adaptation, reduced uterine blood flow, and smaller offspring. It is hypothesized that increasing NO availability could improve placental blood flow, and ameliorate the endothelial dysfunction that occurs with PE, and therefore be used for both the prevention and treatment of FGR or PE. Methods of increasing NO availability include: administration of NO precursors (L-arginine supplementation), use of NO donors (glyceryl trinitrate (GTN)), and inhibition of the clearance of NO or its downstream messengers (phosphodiesterase inhibitors).

L-arginine

L-arginine is an amino acid and the sole precursor to NO. NO production increases with increasing extracellular arginine concentrations, and in patients with cardiovascular risk factors, administration of arginine has improved NO dependent endothelial relaxation. As protein-rich foods are an important dietary source of L-arginine, it has been proposed that a deficiency in L-arginine consumption might contribute to the significant maternal and perinatal morbidity caused by PE and FGR in resource-poor countries.

A meta-analysis of nine studies suggests a beneficial effect of L-arginine on fetal growth. However, this finding must be interpreted cautiously as study quality could only be assessed in 5 out of the 9 studies, data on important clinical outcomes was lacking,

the individual study sizes were small (predisposing to publication bias), and doses and route of administration and treatment duration varied significantly between groups. In contrast, a well-designed double-blinded trial failed to show a benefit of oral L-arginine on fetal growth or markers of NO production.

A randomized controlled trial of L-arginine in combination with antioxidant vitamins demonstrated a 40% reduction in risk of PE in women with a personal or family history of PE. Treatment commenced between 14 and 32 weeks', and it is unclear whether timing of treatment initiation or administration of L-arginine alone will have a significant effect on reducing mild PE. Over half the study participants discontinued their assigned treatment, suggesting that this therapy may not be well tolerated or acceptable for many women.

In summary, there is currently insufficient evidence to recommend L-arginine for the prevention of FGR or PE, and well-designed controlled studies are required. Interestingly, it has been observed that studies are more likely to show a improved outcomes when L-arginine has been used at a low dose, and from earlier in pregnancy. A randomized clinical trial has been proposed to evaluate the effect of arginine supplementation from early pregnancy in resource-poor countries, beginning in early pregnancy.

Nitric oxide donors

There is evidence that nitric oxide donors such as glyceryl trinitrate (GTN) can improve uterine and umbilical blood flow *in vivo*, and *ex vivo* studies have shown GTN to have a protective effect on hypoxia - reperfusion induced apoptosis within the placenta. However, clinical evidence of efficacy in prevention of PE or FGR is lacking. A small prospective double blinded placebo controlled trial using GTN patches as prophylaxis in women at high risk of PE found no significant difference in maternal blood pressure, gestation at delivery, birthweight, or incidence of small for gestational age infants between groups. GTN was started after 24–26 weeks' gestation, by which time the majority of spiral artery remodelling has occurred, and this may have been too late to provide prophylaxis. The side effect profile of GTN, a consequence of its potent venodilatory action, greatly limits the potential for its use as a successful treatment. A study using a higher dose (10mg/24hr) GTN patch in women with gestational hypertension was abandoned after recruiting 16 women; all women randomized to active patches developed severe headache within 6 h and withdrew from the study. An alternative, Pentaerythrityl tetranitrate (PETN), is an organic nitrite which appears to have a more favourable side effect profile compared to other NO donors. As well as its vasodilatory effects, PETN also enhances expression of antioxidant genes, including hemoxygenase-1. A small pilot study suggests that in women with a raised second trimester uterine artery Doppler, PETN reduced the incidences of FGR and perinatal death, but not PE. A larger double blind RCT of PETN vs placebo for the prevention of FGR is currently underway in Germany.

Sildenafil citrate

Sildenafil citrate (sildenafil) is a phosphodiesterase inhibitor with vasodilator properties. Phosphodiesterase degrades the

biologically active second-messengers of NO, resulting in potentiation of NO induced vasodilation. Sildenafil selectively inhibits phosphodiesterase isoform 5, which is found in high concentrations in certain vascular beds, including those within the reproductive tract. Pre-clinical studies, and small case–control studies suggested sildenafil could improve fetal growth. However, a set of well-designed randomized controlled trials (The STRIDER (Sildenafil TheRapy In Dismal prognosis Early onset intrauterine growth Restriction) studies) carried out in the UK, New Zealand/Australia, and Holland have shown that sildenafil does *not* improve fetal growth in severe early onset FGR. Furthermore, the Dutch STRIDER study was halted early following a planned interim analysis, which suggested an increased incidence of persistent pulmonary hypertension in newborns and a trend toward increased neonatal death in the treatment group. It should be noted that these findings were not observed in the completed UK or New Zealand/Australia studies. Due to lack of benefit (and unproven, but possible harm) sildenafil should not be used as prophylaxis or treatment for FGR/PE outside of a research setting.

Improving placental blood flow – vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is an angiogenic growth factor with a potent vasodilator action that plays a significant role in virtually all stages of placental development. Maternal levels of VEGF are significantly lower in FGR pregnancies, compared to gestation matched controls. It is hypothesized that increasing VEGF expression within the utero-placental circulation can improve placental development and utero-placental blood flow, resulting in improved fetal growth. Levels of VEGF can be increased in the maternal uterine arteries using adenovirus gene therapy vectors. A beneficial effect of VEGF on uterine artery blood flow volume and fetal growth has been demonstrated in both small and large animal models, and a prospective observational clinical trial is currently planned to assess the therapy in a clinical setting.

Reducing oxidative stress and inflammation

Melatonin

Melatonin is a hormone produced predominantly by the pineal gland. Although best known for its involvement in regulation of circadian and seasonal rhythms, it is also a potent antioxidant. Melatonin has also been shown to have a direct beneficial effect on vascular function, and has been shown to reduce blood pressure in both spontaneously hypertensive rats, and non-pregnant patients with hypertension. Reduced serum melatonin, and placental melatonin receptor concentrations have been demonstrated in women with PE; these changes may contribute to the increased oxidative stress and resultant endothelial dysfunction observed in PE. Importantly, melatonin has an excellent safety profile with no known serious adverse effects. A phase I clinical trial in women with early onset PE demonstrated that compared to historical controls, women who received melatonin 10 mg three times daily had significantly prolonged diagnosis to delivery interval (average of 6 days), and required less antihypertensive medication. In this study, melatonin reduced oxidative stress in the placenta, and had beneficial

effects on vascular endothelium. Whilst promising, of potential concern is that women receiving melatonin were significantly more likely to have a baby born <10th centile. Therefore, it is important that further studies of melatonin use in pregnancy assess the impact of treatment on fetal growth, as well as maternal outcomes. A randomized controlled trial is currently underway to assess the effect of melatonin on neurodevelopment in FGR pregnancies. In this study fetal growth will be assessed as a secondary outcome.

Statins

Statins are pharmacologic agents that inhibit 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase known for their lipid lowering properties and effectiveness in reducing cardiovascular morbidity and mortality. In addition to their effects on lipid metabolism, statins exhibit a range of other actions that make them biologically plausible candidates for the treatment of PE. These properties include vasodilatory and anti-inflammatory effects, inhibition of anti-angiogenic factors, and upregulation of endothelial nitric oxide synthase.

Pravastatin is the statin most studied in pregnancy, as it is highly hydrophilic, and placental transfer is limited. Animal studies have demonstrated beneficial effects of pravastatin on fetal growth, maternal blood pressure and proteinuria, and an absence of adverse fetal effects. Small observational studies suggest that pravastatin treatment for women with FGR or PE is associated with improved maternal blood pressure and uterine artery flow, prolonged pregnancy and increased birthweight and neonatal survival. One small randomized placebo controlled pilot study of low dose pravastatin from early second trimester was associated with a non-statistically significant reduction in preeclampsia preterm delivery. A pilot study aimed at determining the safety of and pharmacokinetic parameters of pravastatin in pregnant women at high risk of preeclampsia has finished recruiting, and results are awaited with interest.

Plasmaphoresis

Two case reports describe the use of plasmaphoresis to remove free radicals or vasoactive factors from the blood of women critically ill with PE. Plasmaphoresis is expensive and carries significant morbidity and mortality so it is unlikely to be useful in routine clinical practise, although it may eventually play a role in the management of the critically ill woman.

Conclusion

Despite causing significant morbidity, mortality and health expenditure, PE and FGR lack proven effective prevention and treatment strategies which can safely prolong pregnancy and improve outcomes. At best, current preventative measures, such as aspirin and calcium, offer a low-modest reduction in risk to a targeted population. The discovery and study of preventative treatments is hampered by a lack of effective screening tools to accurately identify women at the highest risk of disease, or most likely to benefit from treatment. Many women who do develop PE or FGR appear to lack risk factors for these conditions, and until robust and effective strategies for reliably predicting these pregnancies are in place, preventative treatments will never be comprehensive. Therapies available to treat PE and FGR are even

more limited than those used to reduce the risk of developing these conditions. There are currently no treatments in clinical practice which can improve intrauterine growth or alter disease progression in PE. While some emerging treatments have evidence of biological plausibility and data from human explant and animal studies is promising, rigorous, well-designed studies in both animals and humans are required to establish whether these will be effective, acceptable, and have a beneficial long term outcomes for both mothers and babies. ◆

FURTHER READING

- Costantine MM, Cleary K, Hebert MF, et al. Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. *Obstet Gynecol* 2016; **214**: 720.e1–72017.
- Groom KM, David AL. The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction. *Am J Obstet Gynecol* 2018; **218**: S829–40.
- Hobson SR, Wallace EM, Kingdom JC, et al. A randomized double-blinded placebo-controlled intervention trial of melatonin for the prevention of preeclampsia in moderate- and high-risk women: the MELPOP trial. In: Murthi P, Vaillancourt C, eds. *Preeclampsia. Methods in Molecular Biology* 1710. New York, NY: Humana Press, 2018.
- Hofmeyr GJ, Lawrie TA, Atallah AN, et al. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev* 2014; **6**.
- Magee LA, Rey E, Asztalos E, et al. Management of non-severe pregnancy hypertension - a summary of the CHIPS Trial (Control of Hypertension in Pregnancy Study) research publications. *Pregnancy Hypertension* 2019; **18**: 156–62.
- Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017; **377**: 613–22.
- Weckman AM, McDonald CR, Baxter JB, et al. Perspective: L-arginine and L-citrulline supplementation in pregnancy: a potential strategy to improve birth outcomes in low-resource settings. *Advances in Nutrition* 2019; **10**: 765–77.

Practice points

- There is a paucity of effective prophylaxis and treatment options for FGR and PE.
- Low dose aspirin 100–150 mg nocte should be considered as prophylaxis in women at increased risk of PE or FGR as it appears to give a small reduction in risk of FGR, PE and preterm birth.
- Calcium supplementation should be considered for women at high risk of PE or with low dietary calcium as it appears to halve the risk of gestational hypertension or PE in this group.
- Anticoagulants should not be recommended as part of routine clinical care for reducing the risk of FGR or PE.
- There are many potential new therapies for PE and FGR in development. Rigorous well designed pre-clinical and clinical trials — including long term effects on infant and child health — are required before these can be instituted into routine clinical use.